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THE MANAGEMENT OF ACQUIRED HÆMOLYTIC ANÆMIA*

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IN RECENT YEARS it has been possible to demonstrate abnormal antibodies in the sera of most patients with acquired hæmolytic anæmia. This type of anæmia occurs sometimes in the course of well-defined diseases such as the lymphomas. In many other cases, no such primary disorder can be demonstrated and the cause of the abnormal immune state and excess hæmolysis remains obscure. We are concerned here with the management of patients in this latter group. Blood transfusion, ACTH, steroid hormones and splenectomy are all useful. Our experience with 10 patients treated during the past five years indicates that the use of these measures singly or in combination is successful in most cases.

CLINICAL MATERIAL

There were two males and eight females in this group. Their ages ranged from 13 to 81. The onset was acute in six cases and chronic in four. Acute exacerbations had occurred in two of the chronic cases. Jaundice was present in every case and the spleen was palpable in all but one. Anæmia was severe in every case, with hæmoglobin values ranging from 8.5 g. to as low as 2 g. per 100 ml. Reticulocytosis was present in all. There was leukocytosis in three, leukopenia in three and thrombocytopenia in three. Smears of sternal marrow showed overactive normoblastic erythropoiesis in four. In addition, overactive granulopoiesis was observed in two and lymphoid infiltration in one. Abnormal antibodies were demonstrated in the sera of every case. The direct Coombs test was positive in seven and the indirect Coombs test was positive in one. A high titre of cold agglutinins was present in one case and in the remaining case there was an agglutinating antibody which was active only in the presence of complement. Two cases had increased osmotic fragility of the erythrocytes.

CASE 1.—G.F. This 22-year-old woman was perfectly well until one week before admission in April 1953, when she developed marked fatigue, general malaise, and anorexia, followed by constipation, vomiting and jaundice. On examination, she was markedly jaundiced and had generalized tenderness and tender cervical lymphadenopathy but did not have splenomegaly. On admission the hæmoglobin value was 13.5 g. %, reticulocyte count 1%, bilirubin 0.2 mg. %, Kline test negative, Coombs test positive, osmotic fragility increased, and there were spherocytes in the blood. The bone marrow showed a leukæmoid reaction, and a chest radiograph suggested a bronchopneumonic process in the right lower lobe. Within 10 days the Hb value dropped to 8.5 g. % and the reticulocyte count rose to 9%.

The patient recovered after a period of one month, without specific therapy other than 500 c.c. of blood. The jaundice cleared, she felt well, and was discharged with a Hb value of 12 g. % and 1% reticulocytes. The findings are shown graphically in Fig. 1.

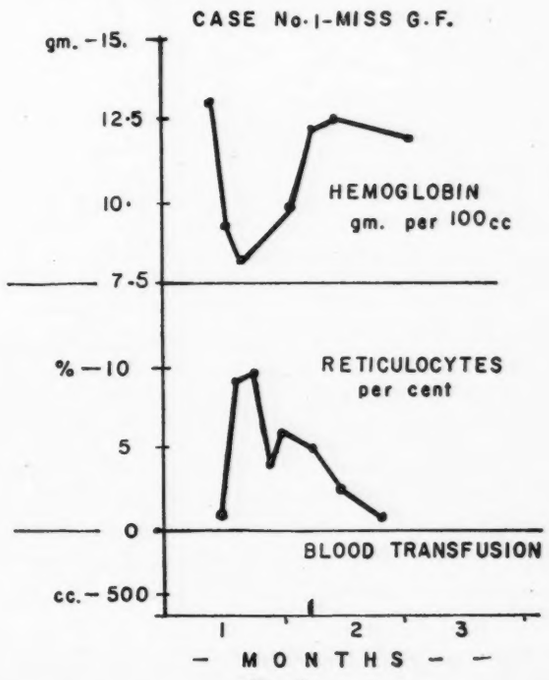

Fig. 1

*From the McGill University Clinic of the Montreal General Hospital, Montreal, Quebec. Presented at the Annual Meeting of the Royal College of Physicians and Surgeons of Canada, Toronto, October 26, 1956.

Comment.—This case of idiopathic acquired hæmolytic anæmia going into remission without specific therapy other than 500 c.c. of blood is very similar to those described by Lederer in 1925.[5] The chest x-ray findings may implicate pneumonia as the etiological factor.

CASE 2.—F.F. This 13-year-old boy was well until 10 days before his admission in June 1954, when he noted the onset of sudden severe headache followed by pallor, weakness, vague abdominal pain and occasional vomiting. On examination he was pale and jaundiced and had an enlarged spleen and liver. The admission Hb value was 6.4 g. %, reticulocyte count 17%, Coombs test positive, bilirubin 4.5 mg. %, and spherocytes were present in the blood. The treatment consisted of blood transfusions and cortisone in dosage of 200 mg. a day. The patient was discharged a week later with Hb value of 8.2 g. % and reticulocyte count of 10%. However, hæmolysis persisted in spite of continued cortisone therapy and the patient was readmitted for further blood transfusions a month later when the cortisone was increased to 300 mg. a day. A satisfactory response occurred with a rise in hæmoglobin value to 9.2 g. %. Starting in September 1954, the cortisone was decreased slowly and discontinued in December 1954, at which time the Coombs test became negative and a return to normal hæmoglobin, reticulocyte and bilirubin levels occurred. The patient has remained completely well since that time. Fig. 2 shows his response to therapy.

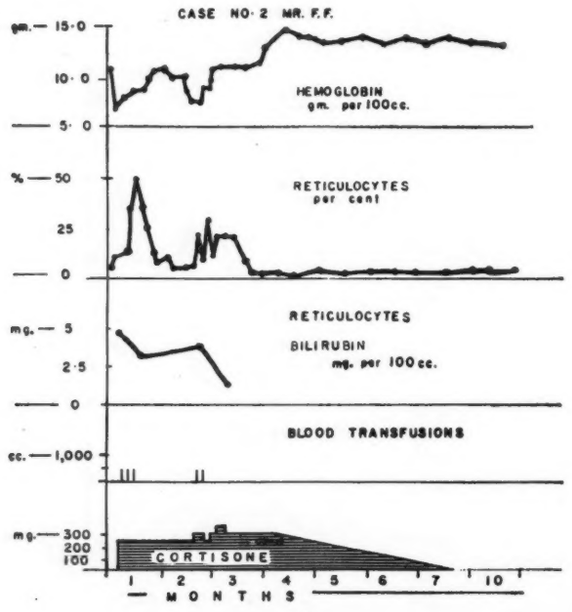

Fig. 2

Comment.—Hæmolysis in this seriously ill boy with idiopathic acquired hæmolytic anæmia was reduced by large doses of cortisone. All evidence of abnormal hæmolysis had ceased and the Coombs test had become negative at the time cortisone was discontinued six months later. No recurrence has been noted.

CASE 3.—C.C. This 61-year-old woman was well until four days before admission in November 1954, when marked faintness and some fatigue were noted. Occasional dark stools had occurred in the past.

On examination she was very pale and jaundiced, and had an elevated temperature. Rales were heard in the lungs. The spleen was not felt. On admission the Hb value was 4.8 g. %, reticulocyte count 45%, Coombs test negative, osmotic fragility normal, and bilirubin 1.1 mg. %. The bone marrow showed extreme normoblastic hyperplasia and the chest film suggested viral pneumonia. Later the spleen became palpable and the Coombs test positive. Cold agglutinins were not found.

The patient was given frequent blood transfusions and started on hydrocortisone (80 mg. daily). Hæmolysis was controlled and the hydrocortisone withdrawn four months later. Eighteen months after discharge the Hb value was 15 g. %, reticulocytes less than 1%, and the spleen no longer palpable. The patient felt well at this time. Fig. 3 shows her course graphically.

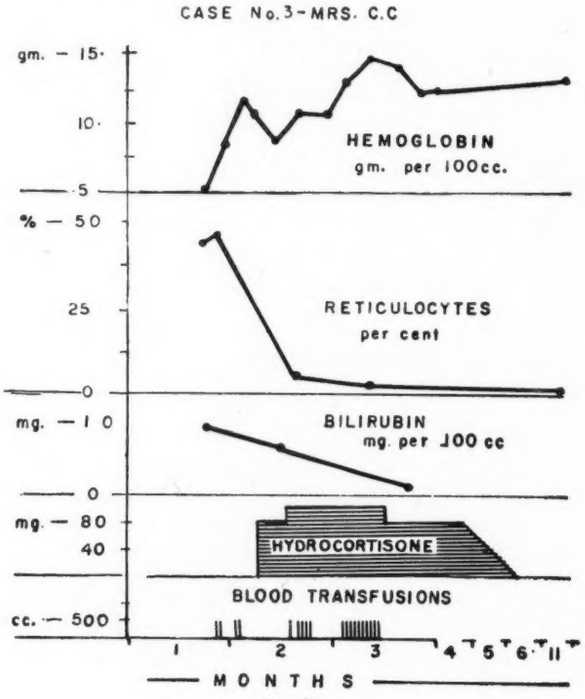

Fig. 3

Comment.—This patient suffered an acute and severe episode of acquired hæmolytic anæmia. The cause may have been viral pneumonia, although no cold agglutinins were found. The episode was controlled with transfusions and hydrocortisone. Complete remission continued after withdrawal of the steroids, and splenectomy was not considered necessary.

CASE 4.—E.D. This 71-year-old woman was first known to be anæmic in 1949, and was admitted during December 1951 with complaints of fatigue, dyspnœa and jaundice for over a year. On admission she was pale and jaundiced, and had enlargement of the spleen and liver. The Hb value was 7.8 g. %, reticulocyte count 30%, bilirubin 2 mg. %, cephalin cholesterol flocculation ++++, Coombs test positive, gastric acidity normal and Kline test negative; bone marrow showed normoblastic hyperplasia.

The patient was started on cortisone 200 mg. daily with a fair response. The dosage was later reduced and finally discontinued one month later. Relapse occurred and cortisone was recommenced. The patient has been on cortisone (between 37.5 and 75 mg. daily) for the past 4½ years. Some hæmolysis has continued, as shown by

the periodic jaundice, high reticulocyte counts and moderately low hæmoglobin levels. However, the patient has continued to feel fairly well and has tolerated the steroids without complication. The course of her disease is shown graphically in Fig. 4.

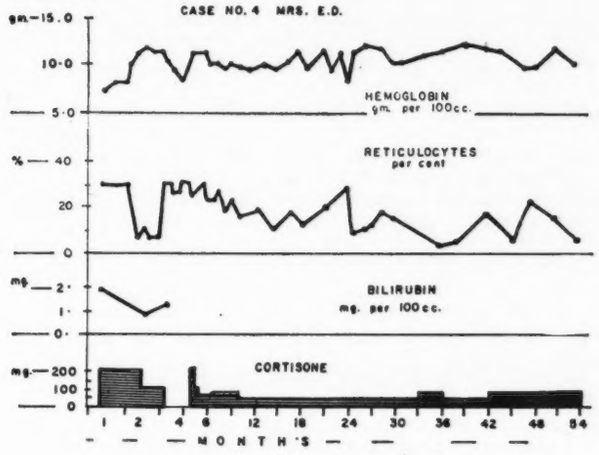

Fig. 4

Comment.—This elderly woman with idiopathic acquired hæmolytic anæmia has been maintained in partial remission on well-tolerated moderate steroid dosage. A complete remission might be obtained by splenectomy. However, we do not feel this to be justified at her age, as her present course is satisfactory.

CASE 5.—W.T. This 81-year-old man was admitted to hospital in 1954, with complaints of marked weakness and severe anæmia of several months' duration for which he had received vitamin B_{12} without benefit. In 1944 he had pneumonia, but was not anæmic or jaundiced. On admission he was pale and had slight scleral icterus, splenomegaly and hepatomegaly. The Hb level was 9.2 g. %, reticulocyte count 6%, bilirubin 1.4 mg. %, Coombs test positive, Wassermann test negative, and osmotic fragility normal; there was achlorhydria and bone marrow showed normoblastic hyperplasia.

He was started on slow intravenous ACTH, 25 u. daily, with a good response. Mental depression developed and the ACTH was discontinued; this was followed by relapse in less than a week. He was then given cortisone 50 mg. daily, the dose being reduced some months later to 37.5 mg. daily. His condition has remained satisfactory on this dose for 18 months, although slow hæmolysis may still be occurring. The findings are shown graphically in Fig. 5.

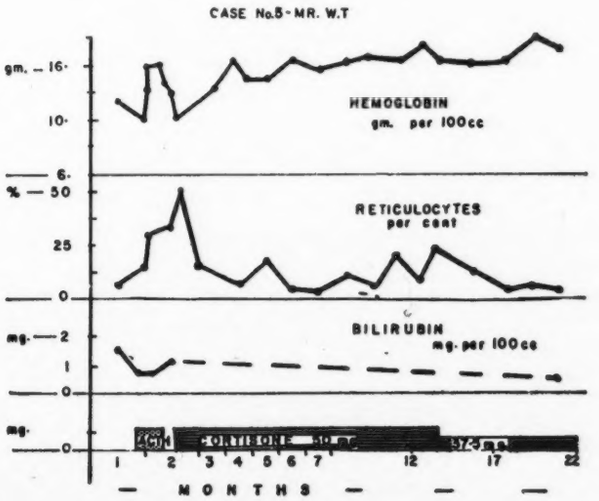

Fig. 5

Comment.—This case of idiopathic acquired hæmolytic anæmia responded satisfactorily to moderate doses of cortisone. As he has tolerated his therapy without complications, operation has been avoided in this elderly man.

CASE 6.—S.S. This 30-year-old woman was admitted to hospital in 1948 complaining of weakness, cough and hæmoptysis. She was pale and jaundiced, and had hepatomegaly, splenomegaly, a low reticulocyte count and a hypoplastic bone marrow. In 1953 she was again admitted, having had tarry stools, epistaxis and a tendency to bruise easily. On the second admission she admitted considerable alcohol consumption and complained of severe bleeding following a tooth extraction. She was very pale, and the liver and spleen were much enlarged. The Hb level was 5.7 g. % and the platelet count 55,000. Results of liver function tests were markedly abnormal and bone marrow was normal. A diagnosis of hepatic cirrhosis, hæmorrhagic diathesis, and possible hæmolytic anæmia was made.

The patient was readmitted seriously ill in 1954, when an ovarian tumour was found. The admission hæmoglobin level was 9.9 g. %, reticulocyte count 2%, bilirubin 0.6 mg. %, liver function tests abnormal, Coombs test negative, cold agglutinins high titre, Wassermann test negative, osmotic fragility normal, radioactive chromium tagged red cell survival 12 days (normal 30-40). The patient was transfused with 4000 c.c. of blood in preparation for pelvic laparotomy, at which time a serous cystadenoma was removed and splenectomy and liver biopsy were performed. The spleen, weighing 640 g., showed marked passive congestion and the liver portal cirrhosis. There was a progressive rise in the hæmoglobin level, the reticulocyte count rose to 8% and the platelet count to 445,000. Eight months after operation the hæmoglobin level was 13.6 g. %, and the red cell survival time was in the low normal range. Epistaxis continued to occur occasionally. The response to splenectomy is shown in Fig. 6.

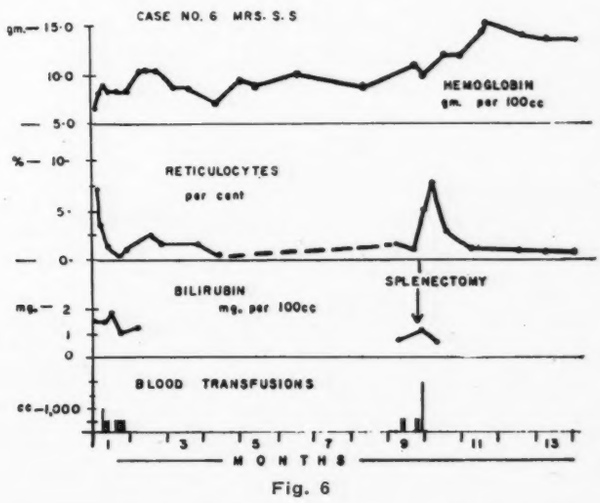

Fig. 6

Comment.—This case was complex, showing hæmorrhage, hæmolysis and possible marrow

depression—the latter suggested by lack of bone marrow hyperplasia during hæmolysis and the increased reticulocytes and platelets following operation. The hæmolysis was probably due to cirrhosis with passive congestion of the spleen, but the ovarian tumour may have been a factor. The excessive hæmolysis has not recurred since splenectomy and removal of the ovarian tumour.

CASE 7.—L.C. This 36-year-old woman was well until a few weeks before admission in 1953, when she had become jaundiced, and had noted severe dyspnœa and some chest pain on exertion. She appeared very pale and jaundiced, and had an enlarged spleen. The admission hæmoglobin level was 2.2 g. %, reticulocyte count 41%, bilirubin 2.8 mg. %, Coombs test negative, and osmotic fragility slightly increased; occasional spherocytes were seen in the blood. An agglutinating antibody active only in the presence of complement was present. She was given 5000 c.c. of blood without appreciable response, and was then placed on cortisone for 40 days with a maximum dose of 400 mg. per day. The hæmolysis decreased, and the hæmoglobin was maintained at a satisfactory level with many blood transfusions. A relapse occurred two weeks after cortisone was discontinued.

Splenectomy was performed in January 1954; the state of the spleen, which weighed 980 g., was compatible with hæmolytic anæmia. Some hæmolysis persisted for five weeks, and two transfusions were required. The patient has maintained good hæmoglobin levels and a low reticulocyte count for over two years since that time. Fig. 7 illustrates her response to therapy.

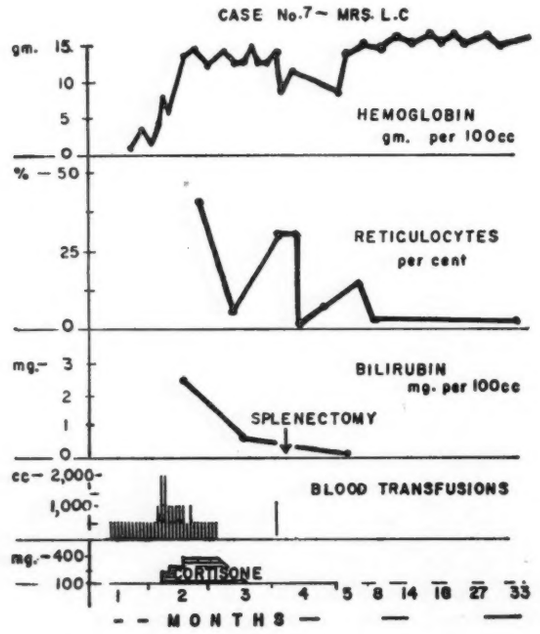

Fig. 7

Comment.—This case dramatically shows the ineffectiveness of transfusions alone in severe hæmolytic anæmia. Steroids were successful in temporarily reducing hæmolysis but a relapse occurred when they were withdrawn. Splenectomy produced a complete and prolonged remission.

CASE 8.—M.C. This 26-year-old woman was admitted early in 1950 with complaints of increasing fatigue of one year's duration and dark urine and stools for two to three months before admission. The patient appeared pale, jaundiced and ill. Splenomegaly was present. The admission hæmoglobin value was 5.5 g. %, reticulocyte count 6.6%, bilirubin 2.2 mg. %, Coombs test positive, Kahn test positive (known treated syphilitic), and osmotic fragility normal; the bone marrow showed hyperplasia. The patient received massive blood transfusions, ACTH both intravenously and intramuscularly, and cortisone in doses of up to 200 mg. a day. Hæmolysis was not well controlled by this therapy. Great difficulty was found in obtaining compatible blood for transfusion. The spleen was removed, weighing 535 g., and its appearance was compatible with hæmolytic anæmia. There was a marked decrease in hæmolysis and one month after splenectomy her radioactive chromium tagged red cell survival time was 29 days (normal 30-40). Three months after operation her hæmoglobin level was 14 g. %, and the reticulocyte count 1.2%. The patient has continued to feel well since that time. Fig. 8 illustrates her course graphically.

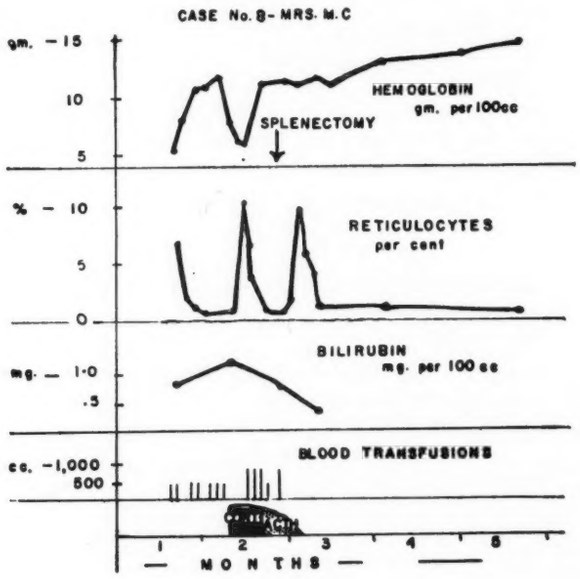

Fig. 8

Comment.—This case illustrates a very severe hæmolytic crisis in a patient with idiopathic acquired hæmolytic anæmia. Hæmolysis was inadequately controlled by ACTH and steroid therapy. Splenectomy was probably lifesaving in this patient and she has remained in remission since.

CASE 9.—V.D. This 56-year-old woman was well until her admission in February 1954, with the complaints of fever, malaise and loss of appetite. On admission she was pale and jaundiced, and had hepatomegaly and splenomegaly. The hæmoglobin level was 7.1 g. %, reticulocyte count 10%, bilirubin 1 mg. %, Coombs test positive, Kahn test negative, radioactive chromium tagged red cell survival time eight days (normal 30-40); the bone marrow showed lymphoid cell infiltration.

Blood transfusions were given, but severe hæmolysis continued. ACTH and then cortisone were administered, with a marked decrease in hæmolysis. Reduction in the dose of cortisone led to uncontrolled hæmolysis, necessitating readmission. Intravenous ACTH, given daily for six weeks, controlled the hæmolysis. A remission without therapy lasted several months, but was followed by a relapse in September 1955, at which time she was readmitted jaundiced and pale. The hæmoglobin level was 5.6 g. %, reticulocyte count 12%; bone marrow showed balanced hyperplasia. Intravenous ACTH and massive blood transfusions were unsuccessful in preventing continued hæmolysis.

The spleen was removed; it weighed 860 g. and its appearance was described as compatible with hæmolytic anæmia. The ACTH was tapered off over two weeks. The hæmoglobin level and reticulocyte count returned to normal and the bilirubin dropped to 0.4 mg. %. She has remained in remission for 10 months since operation without steroid therapy. Recently osteolytic lesions have been reported in the ribs and collapsed vertebræ noted. Her course is illustrated by Fig. 9.

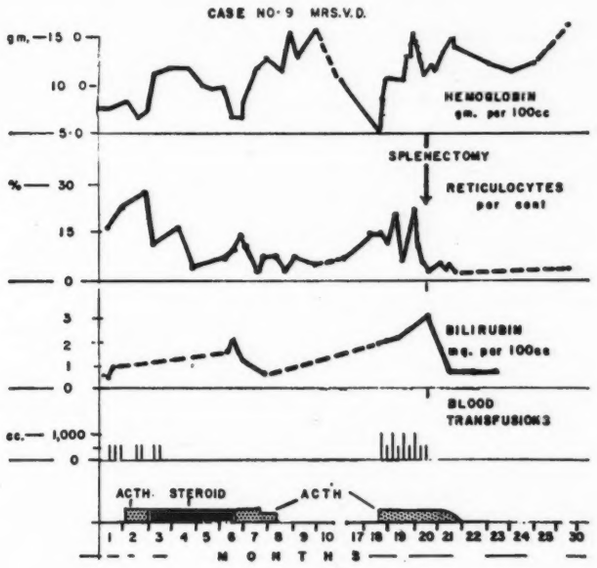

Fig. 9

Comment.—The diagnosis of idiopathic acquired hæmolytic anæmia was made. However, leukæmia or lymphoma cannot be excluded, although these were not reported in the spleen. ACTH and steroid therapy were successful in controlling the hæmolysis during the first two admissions, but proved inadequate during the last. Abnormal hæmolysis ceased after splenectomy.

CASE 10.—G.M. In 1942, at the age of 41, this woman first complained of weakness and fatigue. Pancytopenia was observed in 1945, and she received blood transfusions in 1947 for severe anæmia. Splenomegaly and inguinal lymphadenopathy were noted in 1951. The hæmoglobin value was 11.2 g. %, reticulocyte count 16%, bilirubin 0.3 g. %, Coombs test positive, Kline test negative, and osmotic fragility normal; the bone marrow showed balanced hyperplasia, lymph node biopsy myeloid hyperplasia. Blood transfusions were given. In 1952 the hæmoglobin level was 8.3 g. %, and bilirubin 1.2 mg. %. She received 3000 c.c. of blood.

The following year she was started on cortisone (50-100 mg. daily) with a marked response. A month later she was readmitted with bronchopneumonia and a further severe hæmolytic episode, which was controlled by intramuscular ACTH.

In 1953 she was readmitted seriously ill, pale and jaundiced, with a hæmoglobin level of 5.3 g. %, reticulocytes 17%, and bilirubin 1.2 mg. %. ACTH was started with a good response. However, excessive fluid retention occurred and the drug was discontinued. A relapse occurred and she was given more ACTH. A satisfactory response followed and splenectomy was performed after transfusion with 2500 c.c. of blood. The spleen weighed 950 g. and its appearance was consistent with hæmolytic anæmia. In the following three weeks the reticulocytes, bilirubin and hæmoglobin returned to normal levels, which have been maintained for the past 18 months. ACTH was stopped a few days after operation. The last admission is shown graphically in Fig. 10.

Comment.—This patient had a long history of idiopathic acquired hæmolytic anæmia with recurrent crisis. Hæmolysis was well controlled by ACTH with relapse on withdrawal and excessive fluid retention during the last admission. Splenectomy produced a complete and prolonged remission.

RESULTS

Some data concerning individual cases are presented in Figs. 1-10. One patient (Case 1) had a completé remission after a single blood

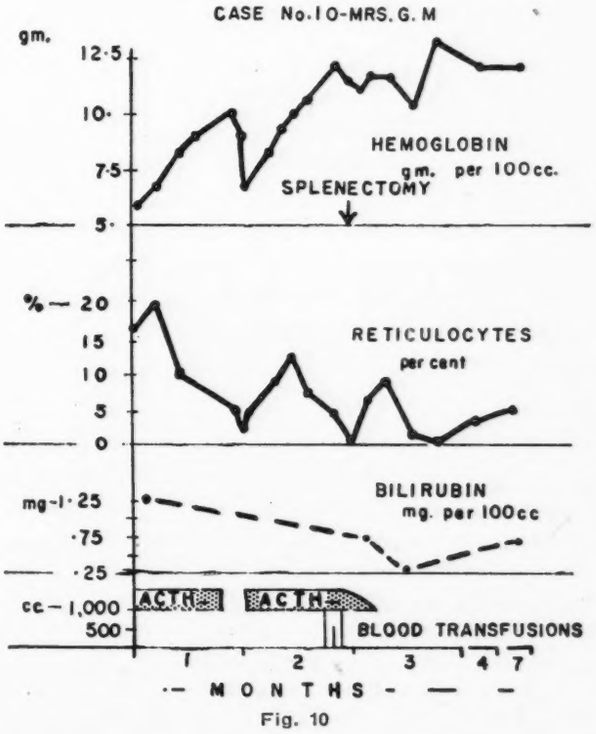

Fig. 10

transfusion. She has remained well for the past three years. Two patients (Cases 2 and 3) had complete remissions during combined treatment

with blood transfusions and steroid hormones. They have remained well for 18 to 22 months after withdrawal of the hormones.

Two patients (Cases 4 and 5) aged 71 and 81 had partial remissions during combined treatment with blood transfusions and ACTH or cortisone. Relapse occurred in each patient when the hormones were withdrawn. Partial remissions were achieved again with hormone therapy. They have been maintained in good health for periods of 18 months and 5 years on small, well-tolerated doses of cortisone.

Five patients (Cases 6, 7, 8, 9 and 10) had complete remissions after splenectomy. They have remained well for periods of 6-24 months which have elapsed since their operations. In Cases 7, 8, 9 and 10, partial or complete remission had been achieved with blood transfusions and ACTH or cortisone. Relapse followed the withdrawal of the hormones. It was not possible to maintain even partial remission with tolerable maintenance doses. Under the circumstances, splenectomy seemed indicated. These patients were prepared for surgery with further blood transfusions and adequate doses of hormones.

DISCUSSION

The course of acquired hæmolytic anæmia is variable. It may be chronic or acute, terminating by spontaneous remission or death. There is no sound basis for prognosis in individual cases and it is difficult to evaluate the results of treatment. Most authors agree that complete or partial remissions can be induced by blood transfusion, ACTH, steroid hormones or splenectomy.[1-17] However, there is no unanimity of opinion concerning the relative values of these methods of treatment when used singly or in combination.

Complete remission occasionally occurs after blood transfusion.[5] More often blood is given to maintain or improve the condition of patients with severe anæmia. In such cases it is sometimes lifesaving. Unfortunately, severe reactions may occur even though the accuracy of cross-matching is not in doubt. The presence of warm panagglutinins in the patient's serum may make it difficult to obtain compatible donor blood. The use of packed red cells and occasionally washed red cells will minimize reactions of this sort. In addition, there is some evidence that these troublesome reactions may be reduced in frequency and intensity when patients are receiving ACTH or steroid hormones.[3, 18]

Experience with ACTH and steroid hormones has been encouraging but the relapse rate is high when the hormones are withdrawn.[1-5, 7, 9-13, 16, 17] No precise dosage schedule has been established but continued large doses are sometimes effective when smaller doses have failed. The use of large doses is limited by the inevitable side-effects. Recent reports suggest that prednisone may prove to be the hormone of choice on this account, especially when intensive treatment is required.[15]

Splenectomy has to be considered when medical treatment is not successful. There is no doubt that many patients improve after the operation. Two recent authoritative series indicate that good results may be expected in more than half the cases after splenectomy. There were six complete remissions in Young's 11 cases[10] while Dacie reported six complete and six partial remissions in 21 cases.[14] Unfortunately, there is no sure way to predict which patients will benefit from the operation.

However, according to recent work[19] detection of a high and progressive rate of autologous Cr^{51} labelled red cell sequestration by measurement of gamma radiation over the spleen suggests that splenectomy will be beneficial, at least temporarily. We have not had any experience with this technique.

CONCLUSIONS

Several useful methods of treatment are available for the management of acquired hæmolytic anæmia, but no clear course of action has been defined to help the physician decide when and how to use these procedures. The plan of management we use is outlined below. It seems reasonable in the light of present knowledge, and the results have been encouraging.

1. Chronic cases in relapse and all acute cases are given ACTH or one of the steroid hormones. In addition, blood transfusions are given cautiously to patients with severe degrees of anæmia. When remission occurs, the hormone is withdrawn slowly. Some patients remain in good health without further treatment.

2. Relapse may occur when hormones are withdrawn. The treatment is repeated and it is sometimes possible to maintain a partial re-

mission with tolerable doses. This compromise is accepted when splenectomy is contraindicated because of the patient's age or general condition.

3. When a remission cannot be maintained without excessive or prolonged therapy, splenectomy is recommended. Success cannot be expected in every case. However, patients not benefited by splenectomy are not handicapped by the operation. It is possible to induce a temporary remission with blood transfusions and intensive hormone therapy in most cases. Surgery is undertaken when this has been accomplished. Hormones are continued during the operation and throughout the postoperative period. Supplements of hydrocortisone are given if there is any indication of impending adrenal crisis during or after surgery. Later, hormones are slowly withdrawn and some patients remain well without further treatment.

We have had no fatalities in patients prepared for splenectomy in this way and we do not anticipate that the mortality rate will be prohibitive as the series increases.

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RÉSUMÉ

Cet article est basé sur l'expérience acquise dans le traitement de 10 cas d'anémie hémolytique d'origine indéterminée suivis à l'hôpital général de Montréal. Les données de la clinique et du laboratoire sont présentées sous forme succinte dans le texte. Bien qu'il existe plusieurs manières d'attaquer le problème aucune règle de conduite n'a pu encore être définitivement établie dans ces cas. Les auteurs suggèrent la méthode qui suit comme leur ayant donné des résultats encourageants.

Les formes chroniques en activité ainsi que les formes aiguës reçoivent de l'ACTH ou une hormone stéroïde. One peut ajouter des transfusions données avec toutes les précautions nécessaires dans les cas d'anémie grave. A mesure que l'amélioration se fait sentir, les hormones peu à peu sont retirées. Certains cas ne nécessitent pas d'autre traitement. Si une rechute se produit on recommence le traitement en conservant cette fois les hormones à dose tolérable. Ce compromis peut suffire si la splénectomie est contre indiquée pour des raisons d'âge ou d'état général.

Lorsque ces mesures ne suffisent plus, il faut avoir recours à la splénectomie. Cette intervention n'apporte pas toujours la guérison espérée, cependant ceux qui n'en retirent aucun avantage n'en souffrent pas non plus. Dans la plupart des cas on peut obtenir un certain répit permettant l'opération, au moyen de transfusions et d'opothérapie intensive. On continue les hormones pendant l'opération et la période postopératoire. S'il y a risque de crise addisonnienne on donne de l'hydrocortisone en doses supplémentaires. Les hormones sont retirées lentement et certains malades continuent a bien se porter. Tous les malades de cette série ainsi préparés ont bien subi l'opération et les auteurs ne prévoient pas de mortalité accrue à mesure que leur nombre de cas augmentera.

PROBLEMS OF ANÆSTHESIA FOR BRONCHOSCOPY*

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MUCH HAS BEEN WRITTEN in recent years on the subject of anæsthesia for peroral endoscopy, especially on bronchoscopy and minor operations on the larynx. Unfortunately most of these publications have appeared in specialist journals of otorhinolaryngology or anæsthesia and only very rarely has this subject been thoroughly discussed in the general medical literature. This seems unfortunate since a considerable number of these procedures are carried out by general surgeons, internists and general practitioners, with varying facilities for anæsthesia. A thorough review and study of the problem therefore seems to be indicated.

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GENERAL CONSIDERATIONS

One overriding problem, which this particular procedure shares with few others, is the fact that the bronchoscopist, by virtue of the procedure itself, must of necessity interfere with the patient's airway. It is true that once the bronchoscope has been passed through the larynx into the trachea, a patent airway is virtually assured unless the procedure is carried out for the re-

moval of a foreign body. However, once the instrument is advanced beyond the carina, a partial obstruction is again produced by the exclusion of the opposite lung, and frequently the upper lobe bronchus of the lung under examination is also occluded. If the procedure is not prolonged and the patient's cardiorespiratory system is not too extensively diseased, this is usually tolerated well. Respiratory obstruction alone because of the surgical manœuvre therefore is frequently not a major problem if laryngeal spasm before and after the procedure can be avoided. However, infinitely more important than respiratory obstruction is interference with adequate ventilation and thus adequate gas exchange across the alveolocapillary membrane. Bronchoscopy is frequently carried out for diagnostic purposes in cases in which this gas exchange is already interfered with by the underlying disease, and the condition is aggravated by the exclusion of a considerable amount of lung tissue during the procedure. It therefore becomes of paramount importance that nothing should be done by the anæsthetist to further complicate the matter through the use of drugs in amounts which would markedly depress respiration by central or peripheral action, since this would interfere further with adequate gas exchange. All agents used in anæsthesia practice for the induction or maintenance of general anæsthesia and for muscle relaxation potentially interfere with pulmonary ventilation. We can think of no more lethal combination in bronchoscopy than the injection of sodium thiopental (Pentothal) with the addition of a muscle relaxant in dosages customarily used in general anæsthesia.

Whatever the anæsthesia, three criteria must be satisfied: (1) The patient must experience no pain; (2) the patient must be sufficiently relaxed to permit accurate pursuit of the objective; and (3) the anæsthetic must be safe.[1]

LOCAL ANÆSTHESIA

Few would disagree with the statement that local anæsthesia is inherently safer than general anæsthesia, and that therefore it should be used in the majority of endoscopic procedures.[2-4] However, it must be appreciated that local anæsthesia in itself carries certain dangers, and these dangers must be fully appreciated.

Unfortunately, the incidence of reactions to local anæsthetics is still far too high and deaths due to this cause still occur too frequently. This is deplorable since local anæsthesia could be the safest procedure, provided those using it are aware of its hazards and limitations, and the nature of reactions to local anæsthesia, their prevention and treatment.[5] Seevers[6] has stated that "there are probably more deaths from local anæsthetics in this country [the U.S.A.] than from any other single class of compounds in common use". Overdose and too rapid administration are the chief causes of toxic reactions. Hypersensitivity is far less frequent.[5, 7]

Basically a reaction from a local anæsthetic will occur if the amount absorbed into the blood stream exceeds the toxic threshold level in terms of milligrams. This toxic threshold varies within certain ranges from one individual to another and from time to time in the same person. But it need never be exceeded if certain safeguards are adopted.

It has been said that barbiturates protect from reactions to local anæsthetics,[6, 8] and this is undoubtedly so. It would seem wise to incorporate one of the barbiturates into the preoperative medication of these patients. The premedication must be adequate to allay fear and apprehension, but not excessive so as to cause respiratory depression. A belladonna derivative such as atropine or scopolamine may or may not be incorporated and this will to a large degree depend upon the procedure for which endoscopy is to be performed. If one of the purposes of the procedure is to remove tracheo-bronchial secretions for examination, it would seem unwise to suppress or inspissate such secretions by the administration of a belladonna drug.

Since the possibility of toxicity is so real with local anæsthetic agents, it follows that their dose must be regulated in a manner similar to that adopted for all toxic agents whatever the route of administration. Hence, a definite amount of solution in terms of milligrams must be measured out, and should not be exceeded in one single administration. If this amount, which the administrator considers safe, is inadequate to provide the depth and extent of anæsthesia necessary for the procedures, some time must be permitted to elapse during which the anæsthetic is absorbed, before a further amount of the agent may be administered. This may mean a waiting period of 15-20 minutes between applications, but this is time well spent in the interest of the patient's safety. The technique of local anæsthesia preparatory to bronchoscopy has been

most ably described by Holinger.[3] We feel very strongly that initially 2 ml. of 2% tetracaine (Pontocaine) or 5 ml. of 1% tetracaine (50 mg.) must not be exceeded.[9] Many physicians—unwisely, we believe—use and recommend single doses exceeding 50 mg. Larger amounts of 0.5% tetracaine would be permissible but despite statements in the literature to the contrary,[4, 9] this has not been found to provide an adequate depth of anæsthesia in many cases. Tetracaine 1% lasts only 25% longer than 0.5% solutions, and some feel that the slight increase in duration does not warrant the increased risk of toxicity of the 1% solution.[10] However, this risk must be accepted in view of the often inadequate depth of anæsthesia with the 0.5% solution.

The same restrictions of dosage which apply to tetracaine apply equally to cocaine, lidocaine (Xylocaine) and hexylcaine (Cyclaine). The total single amount of cocaine should not exceed 300 mg. (3 ml. of 10% or 6 ml. of 5% solution).[9] Jackson[4] has stated categorically that local anæsthesia should be carried out by the transoral route and he is not in favour of the transtracheal block. This technique although satisfactory in some hands has the additional hazard of extratracheal injection, subcutaneous or mediastinal emphysema and infection. Lastly, one should not forget the potency and complete lack of toxicity of "vocal anæsthesia", a very potent adjuvant to any type of regional block.

All investigators state, and it is well to repeat here once again, the importance of knowing exactly how much local anæsthetic one uses and the fractional use of the agent so that the blood level of the agent is not likely to reach toxic proportions, even if absorption should be unduly rapid or unduly large amounts of local anæsthetic needed. Amounts must be measured exactly and amounts used on piriform fossa applicators must also be known. This is best done by running them dry back into a cup, the exact initial content of which has been measured.[9] Gargles with local anæsthetics rarely come into contact with the desired regions and are therefore useless. More important still, they are dangerous. The material may be swallowed and rapid absorption from the gastro-intestinal tract predisposes to toxic reactions.[11]

General Anæsthesia

Those who with us consider local anæsthesia the method of choice will still at times be forced by circumstances to administer some other form of anæsthesia. It may be that a particular physician desires that type of anæsthetic for personal reasons, or that the patient is either unwilling to co-operate or incapable of co-operating in a satisfactory manner to permit examination under topical anæsthesia.

The many different methods and techniques for general anæsthesia suggested in the literature at once indicate that not one single technique in itself is entirely satisfactory. The abolition of protective reflexes, the respiratory depression and the explosion hazard in the presence of flammable agents present problems of great magnitude.

Most investigators now feel that topical anæsthesia should always be carried out in conjunction with general anæsthesia. Macintosh[12] suggests such a combination. Topical anæsthesia is applied while the patient is anæsthetized with sodium thiopental and relaxation obtained with succinylcholine. Morphine and atropine are used for preoperative medication. By the time analgesia is complete, general anæsthesia has become very light and is maintained at this level with intermittent doses of thiopental. Bronchoscopy is therefore carried out under local anæsthesia with the patient very lightly asleep.

Kelsall[13] also gives an intravenous thiobarbiturate, but in very much larger dosage, and uses suxamethonium for relaxation. The apnœic patient's lungs are then inflated with oxygen, and larynx and trachea sprayed with 1% tetracaine. Bronchoscopy is carried out while oxygen is being inflated into the side arm of the bronchoscope; artificial respiration is maintained by the rhythmic manual compression of the patient's chest. If muscle power returns, another small dose of relaxant is given. In an alternative technique he recommends a thiobarbiturate followed by gallamine (Flaxedil) in rather large doses, after which the lungs are inflated with oxygen; this is followed by topical anæsthesia to the cords with 1% tetracaine. He then waits until spontaneous respiration has returned and inflates oxygen with trichlorethylene (Trilene) into the side arm of the bronchoscope. At the end of the operation he administers atropine and neostigmine to counteract residual curarization. Both these methods seem hazardous to us, and the first alternative is certainly highly unphysiological. Any anæsthetic technique which induces apnœa and relies on artificial respiration by compression of the chest is entirely unwarranted.

In some centres the manual compression of the chest is replaced by the use of a mechanical respirator, but this too does not seem a satisfactory method of conducting this type of anæsthesia.

Roberts[1] suggests that after suitable premedication with oral pentobarbital (Nembutal) 90 mg., followed by morphine 8 mg. and atropine 0.6 mg. or scopolamine 0.3 mg. hypodermically 45 minutes before operation, topical anæsthesia is administered three times at five-minute intervals with 2% tetracaine or 10% cocaine. Curare is then injected very slowly intravenously. The recommended dose is 6-12 mg. for the average-sized patient, until the patient can hardly raise the head from the table. He calculates the dose at 3 mg. to every 50 lb. of body weight in healthy adults and 3 mg. for 75 lb. body weight in emaciated patients. As soon as a sufficient state of partial curarization is achieved, sodium thiopental 2.5% is given intravenously very slowly and 60 seconds are allowed to elapse before additional sodium thiopental is given. If there is no respiratory depression, 1-2 ml. increments are given until the lid reflex is abolished. He states that this takes 3-5 minutes and during this time oxygen is also administered.

Others have recommended nitrous oxide and trichlorethylene with a muscle relaxant. It would appear that this technique is superior to one employing intravenous anæsthetic agents since it is potentially much less depressing. On the other hand, induction is slow and not always entirely satisfactory. Jackson[4] circularized a number of clinics, and in the reply to the question, "If you use general anæsthesia, what form do you prefer?" two out of eight said they preferred sodium thiopental, one sodium thiopental with curare and four ether. Were it not for the explosion hazard, ether would certainly be the most useful agent since it can provide adequate relaxation of jaw muscles without undue respiratory depression and it also allows the operator sufficient time to perform his task.

In children no alternative to general anæsthesia exists, since as a rule they are not sufficiently co-operative for topical anæsthesia alone. Here one will often choose the lesser of two evils and employ ether, withdrawing the anæsthetic agent before bronchoscopy is done. In this way an ether-air mixture is contained in the patient's airway; this is a less flammable and less explosive mixture than ether and oxygen. The alternative is one of basal narcosis with rectal thiopental or tribromethanol (Avertin) and maintenance with nitrous oxide-trichlorethylene which may be continued through the side arm of the bronchoscope; this gives quite satisfactory results if one is sufficiently patient to wait until adequate anæsthesia has been induced by this method.

OUR TECHNIQUE

In 1951, Sadove *et al.*[14] described the use of curare in endoscopy where the awake patient would not adequately relax or where muscle spasm was present. We have enlarged on this technique and have made use of the availability of newer agents, which to our mind markedly increase the usefulness and safety of this kind of anæsthesia.

Our technique makes use of the sedative properties of chlorpromazine (Largactil; Thorazine), and uses small amounts of meperidine (Demerol) for sedation and analgesia in conjunction with nallorphine (Nalline). Nallorphine counteracts the medullary depressant effect of meperidine without interfering with its sedative properties. For relaxation we use one of the shorter-acting true curarizing agents, dimethyltubocurarine (Metubine; Mecostrin) and, if necessary, later administer edrophonium (Tensilon) to terminate any residual curarization. Topical anæsthesia is induced while the patient is sedated and relaxed. As an example of our technique the following case is cited:

> The patient was a 202-lb., 52-year-old Cree Indian on whom bronchoscopy had been attempted unsuccessfully under local analgesia alone. The patient understood no English and had a bull neck and a full set of teeth. It had been impossible to obtain adequate co-operation for even visualization of the larynx.
>
> Bronchoscopy and bronchography were re-scheduled for 11 a.m. a few days later. At 8 a.m. he was given chlorpromazine 50 mg. intramuscularly followed at 9.45 a.m. by scopolamine 0.6 mg. He arrived in the operating room very well sedated but not depressed. He was given dimethyltubocurarine 2 mg. intravenously and the effect was observed for two minutes; the dose was then repeated. After a further two minutes he was unable to raise his head from the pillow, yet respiration was in no way depressed. It was now possible to visualize and spray larynx and trachea with 1% tetracaine as a preliminary to bronchoscopy. The cough reflex was preserved and this helped in the spread of the local anæsthetic.
>
> A mixture of meperidine and nallorphine had been previously prepared, using 50 mg. of meperidine with 5 mg. of nallorphine diluted to 5 ml. Before insertion of the bronchoscope he was given 1 ml. of this mixture to increase sedation, and bronchoscopy was started. Since he became a little restless with insertion of the bronchoscope, the merperidine-nallorphine mixture was repeated. Five minutes later, when the jaw seemed to tighten a little on the instrument, dimethyltubocurarine 1 mg. was given and meperidine 10 mg., nallorphine 1 mg. was repeated. Operating conditions were then very satisfac-

tory and there was no evidence of respiratory depression. After completion of the bronchogram, nallorphine 5 mg. was administered to counteract any possible residual depression from meperidine. Since his respiratory function was excellent, it was not felt that an anticholinesterase was needed to counteract dimethyltubocurarine.

This patient by his own admission had no recollection whatever of the operative procedure.

Some explanatory remarks must finally be made. Our technique employs a balanced combination of analgesia, sedation, hypnosis and relaxation. The drugs are balanced in such a way as to cause a minimum of interference with vital functions while yet affording to the patient freedom from anguish and discomfort. For the examiner the technique provides a satisfactory field of operation without the necessity for a race against time. It should be emphasized that the technique makes use of powerful agents, each of which alone is capable of causing just that depression of vital function which this technique is trying to avoid. Each agent or combination of agents must be administered diluted, slowly and in small amounts and the effect observed. Only then should further increments be administered until optimum conditions are attained. We have found dimethyltubocurarine as a relaxant to be superior to succinylcholine (Quelicin; Anectine; Sucostrin). The margin between jaw relaxation and respiratory distress is small with succinylcholine and cannot be maintained with ease even with a continuous intravenous infusion. Alphaprodine (Nisentil) 30 mg. diluted to 10 ml. may be used instead of meperidine. Its tendency to depress respiration and cause hypotension if administered too rapidly by vein calls for caution. It has the advantage of markedly shorter duration of action than meperidine. Levallorphan (Lorfan) may be used in place of nallorphine. We have no personal experience with it, but see no reason why it should not be satisfactory.

SUMMARY

The problems and methods of anæsthesia for bronchoscopy are reviewed.

The indications of local anæsthesia are discussed. Special emphasis is placed upon the potential hazards of this method and how to avoid difficulties. It is concluded that local anæsthesia, properly carried out with due regard to dosage, is the safest method of anæsthesia available at the present time.

General anæsthesia or a combination of general and local anæsthesia should be reserved for those cases which cannot be satisfactorily managed under topical anæsthesia alone. Only in children should general anæsthesia for bronchoscopy be used routinely.

A method is described of balanced analgesia, sedation, and hypnosis, combined with relaxation and local anæsthesia, which the authors have found useful in those cases in which local anæsthesia alone proved unsatisfactory. The method is based on small increments of each agent sufficient to achieve the desired effects without interfering with vital functions and with the patient's own protective reflexes.

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RÉSUMÉ

L'auteur rappelle les problèmes posés par l'anesthésie en bronchoscopie et les différentes méthodes de les résoudre. Il énumère les indications de l'anesthésie locale, non sans mettre en évidence les dangers qui s'y rattachent, tels que la tendance à employer une dose trop élevée d'anesthésique ou à l'administrer trop rapidement. Il indique aussi la manière d'éviter ces dangers, entre autres, en diminuant la possibilité de réaction indésirable par l'addition de barbiturique à la prémédication. Cette forme d'anesthésie, bien conduite, à posologie précise et jamais excédée n'en serait pas moins la méthode la plus sure à l'heure actuelle. L'anesthésie générale seule ou combinée à la locale ne devrait être employée que pour les cas qu'on ne peut aborder autrement. On ne devrait y recourir de routine que pour la bronchoscopie pédiatrique.

L'auteur décrit une méthode basée sur l'analgésie, la sédation et l'hypnose, combinées au relâchement que procure l'anesthésie générale, employée avec succès là ou l'anesthésie locale ne suffisait pas. Cette méthode repose sur des petites doses de chaque agent, suffisant à atteindre l'effet désiré sans cependant diminuer les fonctions vitales y compris les réflexes de défense du malade.

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ASPIRIN ALLERGY*

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A SMALL SERIES of 22 cases of allergy to aspirin seen in our clinic were reported in 1950.[1] Since then further cases have come to our attention and this report records a further 61, making a total of 83 cases seen in the 10-year period (1946-1956 inclusive).

The subject is not new. Robert Cooke[2] first drew attention to aspirin allergy in 1919 and since then there have been many reports of this phenomenon in the literature. Most recently, Samter[5] reported a large series at the Second International Congress of Allergy in Brazil. As aspirin is so commonly used and as true hypersensitivity to it is not uncommon,[12, 14] it seemed proper to draw attention to the problem again. In many reports it has been suggested that aspirin sensitivity occurs only in the severe intrinsic type of asthma and that it has a most unfavourable prognosis. Our experience varies from this in several respects.

In the past 10 years we have seen 4761 allergic patients and have discovered aspirin allergy in 83 or 1.74% of these patients. Of our allergic patients, 2580 had asthma and 78 of these were aspirin-sensitive (3.2%) (Table I). This incidence among asthmatics is of the order suggested by other authors.[6] None of our patients came to us because of known aspirin sensitivity and it was discovered only during our study of the patients or their subsequent care. Symptoms occurred unexpectedly and accidentally in all instances and only came to our attention because of the dramatic and rapid onset of symptoms, often very severe, after the ingestion of aspirin for some such symptom as headache or musculoskeletal pain. It is probable that some of our patients had reacted to aspirin previously but had not recognized the relationship. Many of them had used the drug only sparingly in the past and some seemed to avoid it instinctively.

There is no reliable test of allergy to aspirin other than its ingestion and subsequent observation.[3, 10] Once we had accidentally observed an undoubted causal relationship, we never permitted its use again in such cases for fear of a dangerous result. Cooke and others have reported serious and fatal reactions, and attempts by Mathews *et al.*,[3] Feinberg and Malkiel[4] and others to develop suitable and safe tests have been unsuccessful. Skin tests with aspirin are usually negative and are dangerous.

In all our cases we have accepted the evidence of severe symptoms coming on within a short time of the known ingestion of aspirin and in the absence of any other adequate explanation of the attack. The effects are so dramatic that a causal relationship can hardly be doubted in a particular case. It has been suggested that delayed reactions may also occur, but we have no good evidence of this. That mild and unrecognized allergic reactions to aspirin may occur is realized, but we do not forbid its use in our allergic patients unless we have good reason to suspect it. However, we do try to train our patients to be aware of the possibility of drug sensitivity and to record any untoward effects.

TABLE I.—ORIGINAL COMPLAINTS OF 83 PATIENTS WITH ASPIRIN ALLERGY

Asthma	78
Allergic rhinitis (with polyposis 33)	55
Urticaria	18
Migraine	3
Atopic dermatitis	8
Other drug reactions	13

We attempted to grade the severity of the 78 patients with asthma who manifested aspirin sensitivity as shown in Table II.

TABLE II.—GRADE OF ASTHMA

	Aspirin asthma	*Aspirin urticaria*	*Aspirin rhinitis*	*Total*
Grade I. (Mild)	2	1	3	6
Grade II. (Controlled by simple measures)	29	5		34
Grade III. (Requiring periodic parenteral medication)	10			10
Grade IV. (Very severe with frequent status)	28			28
	69	6	3	78

It will be seen that nine low-grade asthmatics manifested only urticaria or rhinitis when they ingested aspirin but that the more severe asthmatics (Grades III and IV) all manifested asthma with the ingestion of aspirin. It is, however, very interesting also to note that 12 of the 29 Grade II asthmatics developed very severe asthma with aspirin.

*From the Department of Allergy, Division of Medicine, The Winnipeg Clinic. Read at the annual meeting of the Canadian Academy of Allergy, Quebec, P.Q., June 13, 1956.

Aspirin produced asthma in 69 of the 83 aspirin-sensitive cases, rhinitis in 8 and urticaria in 11 cases. These figures may be somewhat confusing unless it is realized that several patients had multiple manifestations of aspirin sensitivity (Table III).

TABLE III.—MANIFESTATIONS OF ASPIRIN SENSITIVITY

Asthma		69
Including rhinitis	4	
Including urticaria	1	
Allergic rhinitis only		4
Urticaria		10
		83 cases

While it is generally held that aspirin-sensitive asthmatics are in the more severe categories,[8, 16] one-third of our cases were not severe asthmatics. However, 12 of these relatively mild cases had alarmingly severe asthma with aspirin.

In the ten-year period of study, 10 of our aspirin-sensitive patients died of asthma, none directly from aspirin (Table IV). Five died previous to 1950 and are in our previous report. The number dying since 1950 (five patients) is smaller proportionately, and this lowered mortality is quite possibly due at least in part to the advent of hormone therapy and also to an increased awareness of the phenomenon with a resultant earlier diagnosis in less severe cases.

TABLE IV.—DEATHS OF ASPIRIN-SENSITIVE PATIENTS

10-year period		*Age at death*	
Males	4	Before 40 years	1 case
Females	6	After 40 years	9 cases
	10		

Before 1950—5 out of 22 cases—mortality..... 22.7%
After 1950—5 out of 61 cases—mortality..... 8.2%
No death was due to aspirin.

Our data were submitted to actuarial analysis. If the 83 patients had been normal, 1.7 deaths would have been expected in the period under study. Insurance experience indicates that the asthmatic population has a mortality about 40% above normal, so that our 83 patients might have had 2.3 expected deaths in the period under review, corrected for age and sex. Thus, our mortality experience with aspirin-sensitive patients is about six times the normal and about four times that expected in the asthmatic population (Table V).

TABLE V.—ACTUARIAL ANALYSIS

Expected deaths in 83 "normal" lives in similar age and sex groups	1.7
Expected deaths in 83 asthmatics of similar age and sex groups	2.3
Deaths in our 83 aspirin-sensitive cases	10.0

The age of onset of aspirin sensitivity was 16-40 years in 37 cases, and over 40 in 46 cases. There was a strong hereditary allergic history in 53 (63.8%). There were 26 males and 57 females, so that in our study, as in others, females exceeded males by more than 2:1.[11] None of our cases were in children,[15] but aspirin sensitivity occurred as often in young adults as in older ones. Allergic heredity is prominent. Eosinophilia of more than 4% occurred in 49 cases (60%).

It is often suggested that the condition in aspirin-sensitive asthmatics is usually intrinsic and non-reaginic.[13] Samter[5] has suggested that aspirin sensitivity does not occur in the extrinsic skin positive cases. While we have noted a tendency for our aspirin-sensitive asthmatics to fall into the intrinsic group, we have seen many whose asthma was definitely extrinsic in character (Table VI). Some of our patients have clear seasonal allergy with or without perennial allergy, and many have demonstrable extrinsic sensitivities (Table VII) as well as infective and other intrinsic factors. Obviously many allergies cannot be classified exclusively as intrinsic or extrinsic (Table VIII).

TABLE VI.—EXTRINSIC ALLERGY

Seasonal allergy (inhalant)	20 cases
Food sensitive by diet trial	19 cases
	39 cases

TABLE VII.—INTRADERMAL SKIN TESTS

No reactions		16 cases
Not tested (severe intrinsic)		4
Not tested (dermatitis)		4
Positive		59
Pollen	42	
Animal	33	
Dust	54	
Total		83 cases

TABLE VIII.—CLINICAL EVALUATION OF ASTHMATICS WITH ASPIRIN SENSITIVITY

Extrinsic factors exclusively	29
Extrinsic and intrinsic	25
Intrinsic	24
Total	78

Aspirin is the original trade name for acetylsalicylic acid. The clinical sensitivities reported here occurred only with this substance. It was taken under a variety of names and in a variety of compounds. Patients must, of course, be warned of the many preparations containing aspirin. It is interesting that these patients all tolerate acetamide and sodium salicylate, and many have used one of the acetamide compounds as analgesics without difficulty.

SUMMARY

1. Aspirin sensitivity occurs in a small, but notable, fraction of the allergic population (3.2% of our asthmatics).

2. Allergic reactions to aspirin are often severe and may be dangerous even in otherwise moderate allergic disease.

3. Females manifest aspirin sensitivity twice as frequently as males. Family histories of allergy are frequent (64%). Eosinophilia is common (60%).

4. The phenomenon has not occurred in children in our series.

5. Allergy to aspirin is not confined to the intrinsic or non-reaginic group of allergies or to the severe cases. In fact, it occurred with equal frequency in both extrinsic and intrinsic types.

6. The over-all mortality in our series is high (at least four times the expected mortality in the asthmatic population) and it seems justifiable to conclude that when aspirin sensitivity occurs in severe asthmatics a poorer prognosis is indicated.

7. Aspirin sensitivity was most frequently manifested by asthma but also produced allergic rhinitis and urticaria in some. We did not encounter other forms of aspirin sensitivity.

8. Variations of the aspirin molecule change its allergenic property.

We desire to express our appreciation of the valuable assistance given us by the Actuarial Department of the Great-West Life Assurance Company.

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RÉSUMÉ

L'hypersensibilité à l'aspirine se retrouve chez un petit nombre de malades, plus souvent chez les femmes que chez les hommes, et peut entrainer des conséquences graves, même si les manifestations d'allergie à d'autres substances ne sont que légères. Elle s'accompagne d'éosinophilie et se manifeste aussi bien dans l'asthme intrinsèque que dans l'autre. Comme l'auteur l'a déjà fait remarquer ici antérieurement, (*Canad. M. A. J.*, 64: 187, 1951) la mortalité chez ces malades est plus élevée que celle de la population asthmatique en général. L'aspirine peut aussi donner lieu à de la rhinite et à de l'urticaire. Une légère modification à la formule moléculaire de l'acide acétylsalicylique peut suffire à lui faire perdre ses propriétés antigéniques.

DERMATOMYOSITIS

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UNVERRICHT gave dermatomyositis its name in 1891. It was described by him and two other authors in independent reports in 1887. Nevertheless controversy still continued in the German literature as to whether dermatomyositis was clearly separable from suppurative myositis. Acceptance of the condition as a distinctive pathological entity probably dates from Fahr's description in 1921 of a single case in which the triad of pathological features was illustrated in colour—degeneration of muscle, vasculitis and degeneration of collagen.[1] Since then the conception of dermatomyositis is bound up with its inclusion in the diffuse collagen diseases. Dermatomyositis takes its place in the group because the hallmark of the disease is fibrinoid degeneration of collagen, and because cases occur which are intermediate between dermatomyositis and other members of the group.[2-8]

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Despite many communications indicating reasons for including dermatomyositis in the collagen diseases, there is only one critical account of the pathology in the English language. It is by Pagel, Woolf and Asher, and deals only with relatively late appearances in the fatal case in a boy and in two adults.[7] There are a number of reviews of the condition in the American literature but we have not found any communication with a critical account of the pathology, and none clearly illustrates fibrinoid necrosis of connective tissue in the muscle. In a recent review of the condition Domzalski and Morgan[9] state that the changes in muscle are not specific.

The findings are summarized in Table I. In some cases the relative preponderance is indicated by numbers of pluses; this is the authors' relative evaluation. All but one of the cases were visited shortly after the diagnosis was made. The findings are compared with the review of Wedgwood, Cook and Cohen[2] of 26 cases of dermatomyositis in children in Boston. Where the present findings differ, this is indicated.

Sex.—Our preponderance of girls, 6 in 8, was higher than in the Boston series, 15 in 26.

Social status.—Two of the cases were associated with poverty at home.

Onset.—The Boston workers emphasize the insidious nature of the disease. Case 4 was treated for stomatitis with mouth washes and sulfonamides, and the disease, presenting mainly as an erythema, which developed during treatment, may have been a drug reaction. Case 7 had a history of an acute febrile illness necessitating five days in bed, and the parents date a history of six months of increasing weakness from this illness. The remainder were insidious.

TABLE I.—DERMATOMYOSITIS

No.	*Name*	*Age at onset*	*Sex*	*Year*	*Muscular weakness*	*Erythema*	*Œdema*	*Periorbital œdema*	*Severe sore throat or stomatitis*	*Subcutaneous nodules*	*Nodules—mouth and tongue*	*Fever*
1	Studley	6	M	1950	++++	++++	++++	++++	+	—	—	+
2	Newell	1 10/12	F	1950	+	+++	++++	+	—	—	+	+
3	Gallant	10	F	1952	+++	++++	++++	+++	—	—	—	—
4	Gill	5	F	1953	+	++++	—	—	+	—	—	—
5	Craig	6	F	1950	++	+++	++	++	—	—	—	+
6	Richardson	1 8/12	M	1954	+++	+++	+++	++	—	—	—	++
7	Anthony	13	F	1953	+++	+	?	—	—	+	—	+
8	(1) Lantz (1, 2)	11 15	F	1950 1954	++ ++	++ +	+ —	— —	+ —	— +	— +	+ +

It is our purpose in this communication to survey the clinical histories and pathology of eight cases which the authors have collected in a five-year period, October 1950 to November 1955, in Nova Scotia, and to emphasize the severity and individuality of the lesions which give rise to the disease.

CLINICAL MATERIAL (Table I)

The eight cases in this report occurred in white children between the ages of 18 months and 13 years; one girl of 11 had a relapse at 15 years. All except one were initially admitted to the Children's Hospital, Halifax, and the diagnosis in all cases was confirmed by biopsy.

Cases 1, 3, and 6 concern acutely ill and very sick children with the triad of brawny œdema, marked muscular weakness, and skin rashes. Case 5 was similar but with much less general toxæmia. Case 2 was that of an irritable infant with generalized brawny œdema and rashes. Case 4 was in a child with conspicuous skin rashes and some awkwardness in walking. Cases 7 and 8 were in older girls with marked muscular stiffness and weakness.

Recurrent severe sore throat was a feature of Cases 1 and 8; in Case 1 over a period of 6 months, in Case 8 almost continuous for seven weeks so that the girl lost much weight from starvation. The other symptoms developed insidiously during the episodes of sore throat.

Muscular weakness.—One infant, Case 2, was listless and irritable, and at the age this is as far as one can go in assessing minor muscular weakness. In the remainder, muscular weakness was conspicuous except for Case 4. In Cases 1 and 6 it was so severe that the patients could not sit up in bed. In the rest, weakness involved the legs in all, and variously also the arms, shoulder girdle and neck, and in one case also the lips. The weakness was usually first noticed as difficulty, slowness or awkwardness in walk-

ing or difficulty in climbing stairs. In Cases 7 and 8, stiffness was a prominent feature, of the legs in 8 and of legs and arms in 7. Case 7 had some spasm of the legs, and in Case 8 the legs could be extended only with difficulty. Case 3 had difficulty in swallowing. Weakness of the muscles of respiration was not noted; it was a determining factor in some deaths in the Boston series.

Erythema.—Rashes varied from bright red to dusky red and even blue, macular to blotchy to confluent. Frequently the affected skin was dry and scaly, sometimes apart from the rashes. The distribution was very variable and involved face, trunk and limbs. The intensity varied from gross to slight. The Boston workers emphasize a predilection for extensor surfaces of limbs and near or over joints. The rashes on limbs were usually on extensor surfaces, and in three cases were particularly over joints. Rashes varied from time to time, and in four cases were the first sign noted by the mother. In two cases (7 and 8, second admission) erythema was confined to small areas over subcutaneous indurations, and in one case (4) a confluent rash about the face was the main clinical sign. Chronic skin changes with pigmentation and depigmentation, as noted in the chronic cases of the Boston series, were not features in our series, which are mainly acute.

Œdema.—A non-pitting thickening of the skin was noted clinically in six cases, and was generalized in four. In Case 5, it was looser and the child lost 7 lb. during the 18 days in hospital with reduction of the œdema. In Case 8 (first admission), there was swelling of one side of the face for a few days but no other evidence of œdema. In Case 7, noted as having no œdema, the girl was chubby, and considering the biopsy appearance it can be taken that there was generalized slight thickening of the arms and legs.

Face.—Alteration of the face was common. Swelling also was common, particularly around the eyes and forehead—not always symmetrical, sometimes brawny, sometimes pitting, and so marked in Cases 1 and 3 that they could not see in the mornings. Rashes were more common about the eyes and forehead than on any other site.

Nodules.—Scanty, widely distributed, subcutaneous thickenings were present, as small nodules in the panniculus (Case 7) and as flatter, more superficial indurations (Case 8, second admission). Both showed no clinical œdema, and erythema was strictly confined to the skin overlying the indurations. Bluish nodules were present in the tongue and inside the cheeks in two cases. Nodular lesions are not mentioned by the Boston workers.

Swollen joints were present in one case (Case 8).

Fever.—A low-grade intermittent fever was present in all cases at some time, but a temperature of 103° F. or more was a feature only in one case (Case 6), where the temperature on admission was 105° F.

Lymphadenopathy, general or only cervical, was noted in six cases but was not conspicuous.

Mouth.—One case had stomatitis; in four cases injection of the fauces was noted and five had dental caries. In one case the gums bled readily.

Pain.—Generalized tenderness was not an outstanding feature; attempts to extend the legs were painful in Case 8 (first admission). One patient (Case 2) was very irritable. Case 7 was free from pain despite marked disability.

Extra-integumental involvement.—There was no evidence of cardiac or respiratory involvement in any case. Case 1 had a swollen abdomen, and may have had vascular involvement outside the skin and muscle. Case 8 was thought on first admission to have carditis but time has not substantiated this.

Laboratory findings.—Leukocytosis or eosinophilia was not a feature in any case. Five of the Boston series had an eosinophilia. The sedimentation rate was elevated in all but one case. Mild anæmia was a common feature. Throat swabs in cases with sore throat and stomatitis yielded no special information. Urine was normal in all cases, except Case 8 (first admission) where there was heavy but transient albuminuria. Special biochemical and serological investigations were not carried out, but the Boston workers report no special findings.

Treatment and Outcome (Table II)

While in hospital the patients for whom antibiotics are indicated in Table II were under one or both most of the time. In addition special supplements of vitamin C and a low salt diet were generally given. The patients were followed up until November 1955.

TABLE II.—DERMATOMYOSITIS: TREATMENT AND OUTCOME

Case	*Clinical condition*	*Drugs*	*Days in hospital*	*Condition on discharge*	*Outcome*
1	Acute, grave	Aureomycin, penicillin	70	Much improved	Healthy
2	Acute, serious		14	Little improved	Ill for one year, now healthy
3	Acute, grave	Cortisone (39 days), aureomycin, pencillin	62	Unimproved	Died at home 2 months later
4	Mild ? drug reaction	Aureomycin	14	Much improved	Quick recovery, healthy
5	Acute	Penicillin, aureomycin	18	Improved	Slow recovery, healthy
6	Admitted *in extremis*		4	Died in hospital	
7	Subacute to chronic	Cortisone	28	To continue treatment at home	Cripple
8 (1)	Subacute	Aureomycin	42	Improved	Well between relapses
(2)	Subacute	Penicillin, cortisone	26	Much improved	Well

It is evident that the disease can be self-limiting without treatment. Case 2 was taken home at a time when she had generalized brawny œdema. She was nursed at home without drugs. Her family doctor visited her regularly and reported that she was restored to normal health after a year of sickness. Now, four years later, she is a normal healthy child. Case 5, after only 18 days' treatment, was nursed at home and ultimately was restored to full health.

Case 1 was in the same category of severity as the two fatal cases, and muscle biopsy confirmed gross disease. Nevertheless, he is now a healthy normal child—altogether a remarkable outcome. He received a long course of antibiotics.

There was only one relapse (Case 8) with an interval of over three years of apparently normal health. Case 7 is the only one to remain a permanent invalid. She now has atrophy and sclerosis of the limbs and shoulder girdle, with almost board-like rigidity of the legs. Radiological examination has recently revealed gross calcification, especially in the legs.

Treatment is discussed fully by the Boston workers. Our impression is that the clinician should make the assumption, as in rheumatic fever, that the disease is of an allergic nature and possibly streptococcal in origin, and that prolonged antibiotic treatment may prevent recrudescence. In all cases necessary dental treatment was carried out as soon as the patient was fit. Our findings are much less gloomy than those previously reported in the American literature.

PATHOLOGY

Material.—Two biopsies were available from Cases 7 and 8, and one from each of the remainder. Two were from the deltoid muscle, one was from the calf, and the remainder were from the middle of the thigh. In only one case was the specimen small (Case 8, first admission), and in five cases large wedges of skin and muscle were removed for critical study. A small amount of material from each case was processed by the usual routine method for surgical tissues, and in all but two cases changes essential to the diagnosis were made out. The remainder of the tissue in each case was fixed and processed by slower methods. In all cases a diagnosis of collagen disease was made, involving the triad of vasculitis, degeneration of muscle, and alteration in collagen. While varying quantitatively, the changes in all cases were essentially similar (Table III).

TABLE III.—DERMATOMYOSITIS: LESIONS OF SKIN AND MUSCLE

	Acute cases						*Subacute to chronic cases*		
	1	*2*	*3*	*4*	*5*	*6*	*7*	*1—8—2*	
Fibrinoid necrosis of connective tissue	++++	+	++++	+	++	++++		++	+++
Hyalin necrosis of muscle	++++	+	++++	+	+	++++	+	—	+
Sarcolysis	++++	++	++	—	++++	—	+++	—	—
Vasculitis	++	+	+	+	+	+	+	+	+++
Pannecrosis of muscle	++	—	++	—	—	—	—	—	—
Fibrosis of muscle	+	—	+	—	+	+	++++	+	—

Fig. 1

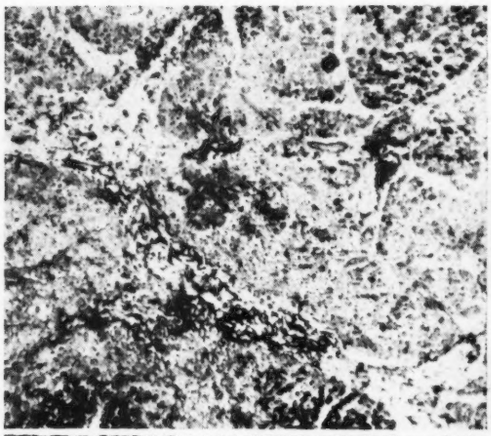
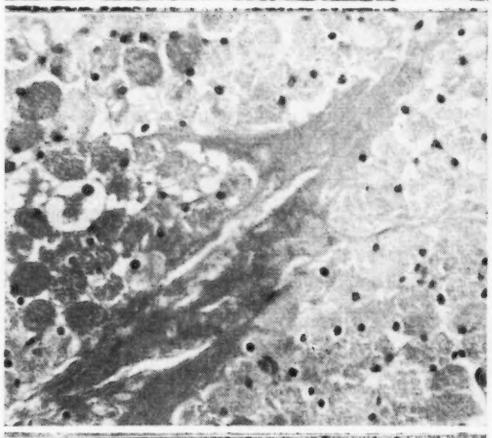


Fig. 2

Fig. 3



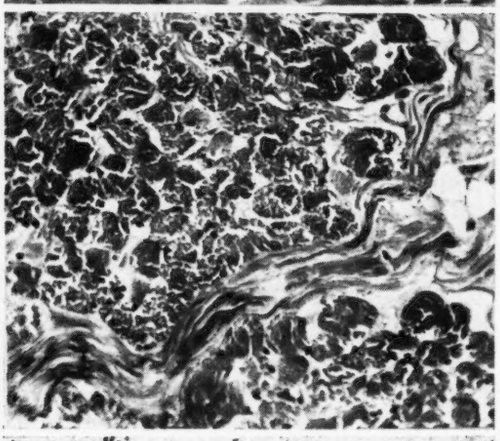
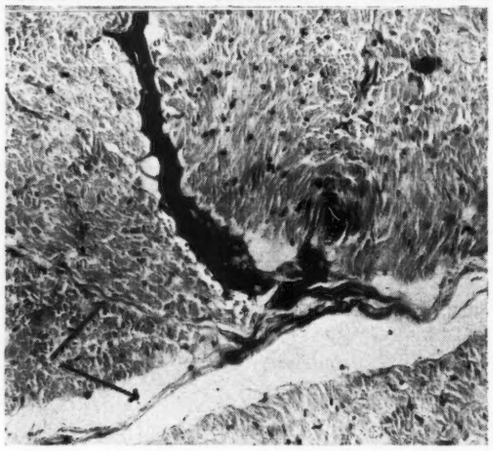


Fig. 4

Fig. 5



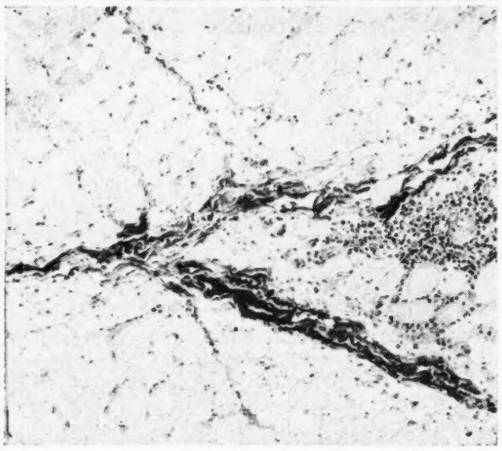


Fig. 6

Fig. 1 (Case 3).—Pannecrosis; connective tissue planes are grossly swollen by œdema and the collagen is replaced by a fibrinous infiltrate. The muscle is almost completely lysed (Iodine-Mallory). **Fig. 2** (Case 8, first admission).—Fibrinoid necrosis; the perimysium is grossly swollen and disorganized (Hæmatoxylin and Eosin). **Fig. 3** (Case 5).—Fibrinoid necrosis; the connective tissue is grossly swollen and appears as a "liquid" infiltrate filling the interstices. The muscle is undergoing lysis (Hæmatoxylin and Eosin). **Fig. 4** (Case 1).—Fibrinoid necrosis; the connective tissue is grossly swollen and disorganized. The darker areas represent fibrin-staining (Iodine-Mallory). **Fig. 5** (Case 1).—Fibrinoid necrosis; when stained for fibrin, the swollen connective tissue has all detail obscured by the reaction (Black); compare with normal collagen indicated by the arrows (Saline-Gram). **Fig. 6** (Case 7).—Fibrinoid necrosis; note the inserts of material staining as for fibrin in the line of the connective tissue planes. There is round-cell infiltration around a small area of vasculitis (Saline-Gram).

Changes in Muscle

Pannecrosis.—In the most severe reactions observed in this study there were areas of inflammatory œdema and fibrin infiltration with widespread degeneration of muscle, lytic and waxy (Fig. 1).

Degeneration of collagen.—Degeneration of collagen was gross and varied from acute fibrinoid necrosis to hyalin degeneration. Despite many reports to the contrary, the authors have not found any better representation of fibrinoid necrosis in collagen than in the muscles of

Fig. 7

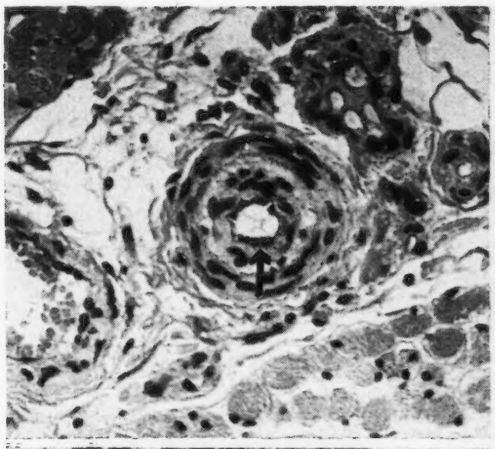


Fig. 8

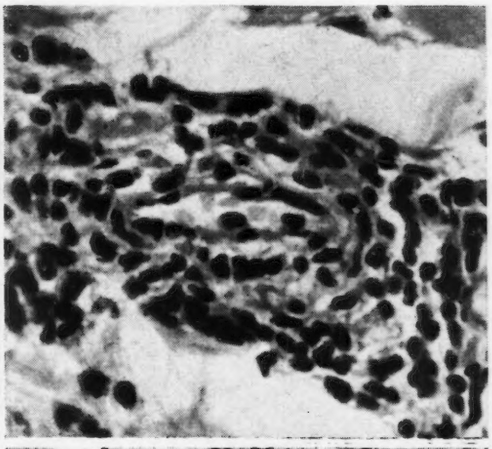


Fig. 9

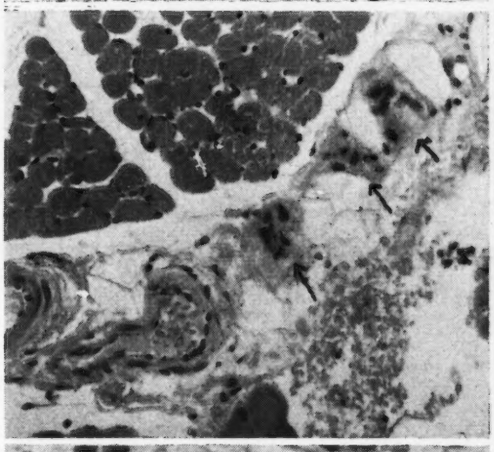


Fig. 10

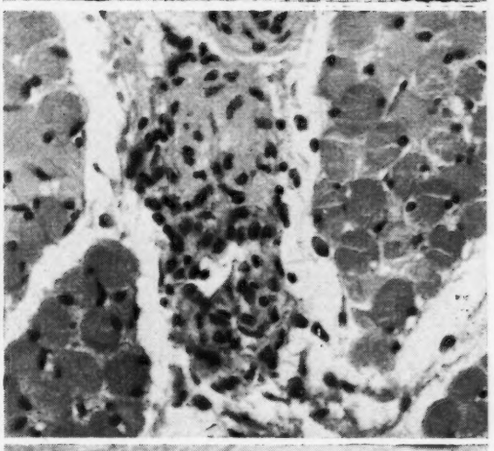


Fig. 11

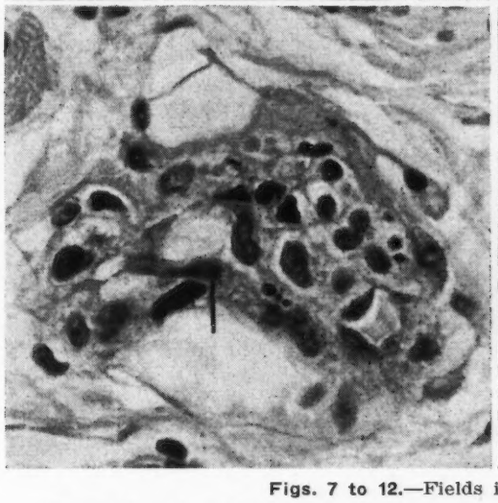
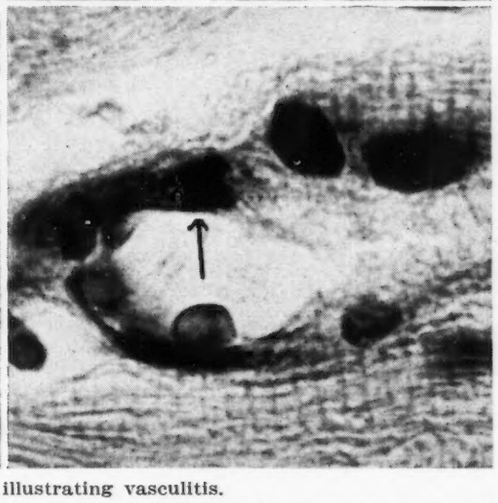


Fig. 12



Figs. 7 to 12.—Fields illustrating vasculitis.

Fig. 7 (Case 1).—Shows a small artery with proliferation of subintimal cells, and increase and radial arrangement of endothelial cells (arrow). **Fig. 8** (Case 5).—Shows a small vessel surrounded by a cuff of mesenchymal cells, while the endothelial cells are prominent and there is proliferation as a bud projecting into the lumen. **Fig. 9** (Case 2).—The arrows point to a small vessel, the lumen of which is obscured by endothelial proliferation. **Fig. 10** (Case 5).—A small vessel is surrounded by mesenchymal cells embedded in degenerate connective tissue. **Fig. 11** (Case 5).—Mesenchymal cells cuff a small vessel whose lumen is indicated by an arrow. **Fig. 12** (Case 2).—A capillary in muscle showing an endothelial cell in mitosis (arrow). All Hæmatoxylin and Eosin.

dermatomyositis. Duff[3] has given a clear description of fibrinoid necrosis of collagen, and the changes described by him were easily discernible in hæmatoxylin and eosin (H. and E.) sections of our material. In some areas bands of collagen were seen to be grossly swollen and altered (Fig. 2), and beyond this change the collagen had a liquid appearance as if flowing into the interstices of the tissue (Fig. 3). In this state the material gave strongly positive reactions with routine stains for fibrin (Fig. 5). Fibrinoid necrosis is not, however, always uni-

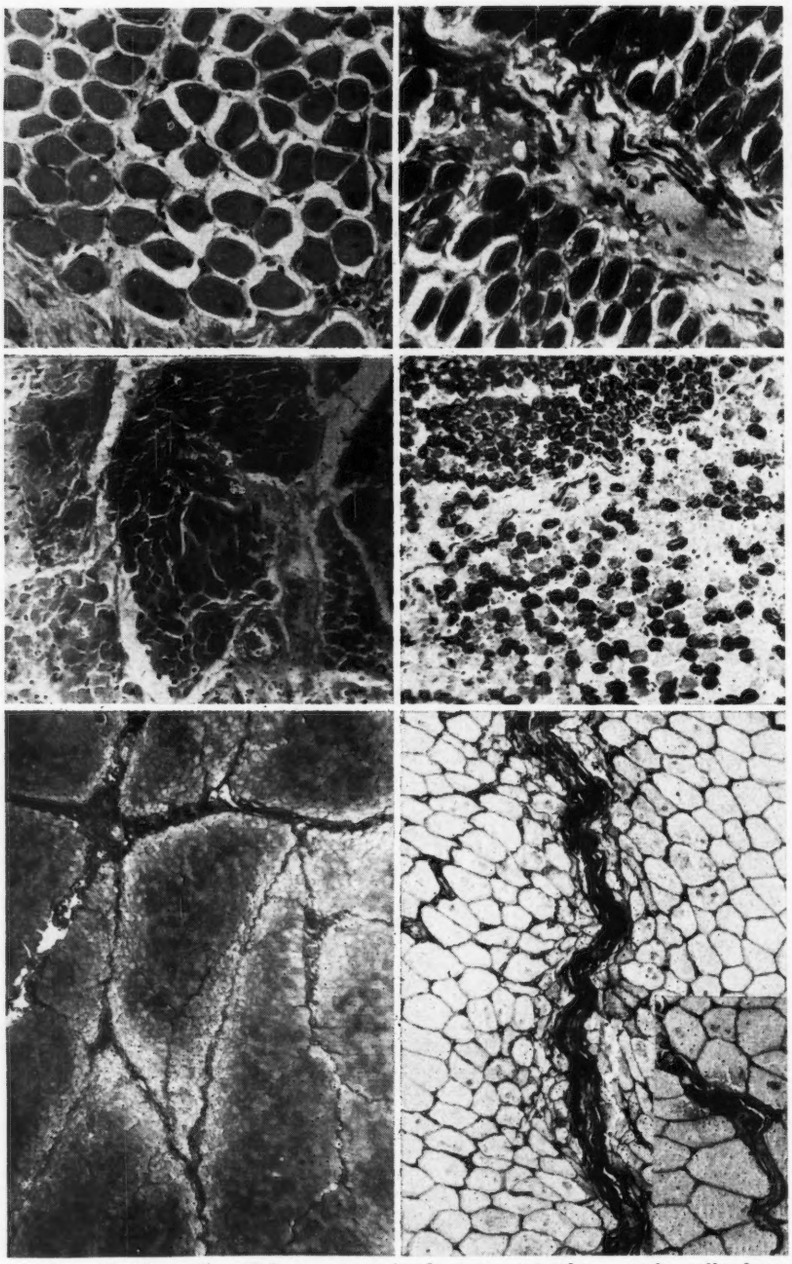


Fig. 13 (Case 1).—Œdema, unstained, separates the muscle cells from the connective tissue framework (Hæmatoxylin and Eosin). **Fig. 14** (Case 3).—Granular œdema separates swollen, interrupted collagen fibres which are cast in fibrin (Iodine-Mallory). **Fig. 15** (Case 1).—Hyalin necrosis of muscle presenting in the centre as an infarct-like wedge (Hæmatoxylin and Eosin). **Fig. 16** (Case 2).—Lysing muscle shows as pale fibres, and "fibrinoid" appears as black inserts in the line of the connective tissue plane (Iodine-Mallory). **Fig. 17** (Case 7).—A regular pattern of lysing muscle (pale) abuts on thickened connective tissue planes (Iodine-Mallory). **Fig. 18** (Case 7).—The connective tissue plane is grossly thickened and this is made up of collagen fibrils (black) and hyalin (paler areas). The small insert shows more condensed hyalin (pale band) with a few fibrils (black) in its substance. The hypertrophied muscle is unstained, contrasting with the intact connective tissue framework (Reverse-Gram).

form and varied appearances are shown in Figs. 4, 6 and 16. Thus, some of the collagen was swollen and degenerate, but contrasting with other areas which stained as for fibrin with routine stains.

Hyalin degeneration.—All stages could be seen between acute fibrinoid necrosis and a state where the collagen was swollen, uniform, and acellular. The swollen bundles were glassy, stained fainter than connective tissue, and did not give positive reactions for fibrin. This can be described as a hyalin degeneration. With appropriate methods the hyalin was seen to contain reticulin fibres running longitudinally, sometimes as small abrupt insertions (Fig. 18). The appearances suggested that it was a phase in recovery from the acute degeneration of Figs. 3 and 5, where the "liquid" collagen had condensed and reticulin fibrils were being reconstituted in the matrix.

While degeneration of collagen was generally conspicuous in areas showing severe muscular degeneration, it was also frequently present in whole sections where the muscle appeared normal or showed a minimum of damage. In Case 8 (first admission) the biopsy specimen of muscle was small. While there was gross fibrinoid necrosis of the epimysium, the underlying muscle appeared normal (Fig. 2).

Fibrosis. — Increase of apparently normal collagen along the connective tissue planes was also a feature but gross scarring was not a feature in any case, except Case 7.

Œdema. — Interstitial œdema was a constant feature in the zones of acute reaction. The bulk of the fluid was usually unstained, but a dense, finely granular material was also apparent, variously separating apparently normal collagen fibres, broken curled fibres staining normally or weakly for collagen or strongly fibrinoid. In some cases it showed metachromatic staining reactions and it may represent altered ground substance, but on the whole it was indistinguishable from the material in severe inflammatory œdema. Intense fibrinoid

necrosis of connective tissue could be manifest without evidence of œdema (Figs. 13 and 14).

DEGENERATION OF MUSCLE

1. *Waxy degeneration.*—In all cases exhibiting degeneration of muscle, examples of the familiar waxy or hyalin necrosis were present where the fibres and their sarcolemmæ were swollen, fused and acidophilic, and nuclei were pyknotic or absent. This occurred in single scattered fibres, in small groups, and occasionally as a segment suggesting an infarct secondary to vascular damage (Fig. 15).

2. *Sarcolysis* was, however, a more conspicuous phenomenon except in muscle showing the most severe forms of damage. In this condition the connective tissue was intact, and the myofibrils were seen to be separated by œdema, and then to undergo lysis, leaving the sheath filled with a faintly staining granular material. The nuclei of the affected fibres increased in number, became prominent, and appeared finally in the centre of the fibre. There appeared to be an acute and a chronic form. In the former, nuclei underwent either rapid lysis or pyknosis. In the latter the nuclei were sometimes normal but more commonly were large and vesicular, often with a prominent nucleolus, and sometimes increased in number. The swollen fibre gradually collapsed, and the nucleus disappeared. In longitudinal section these changes affected only part of the muscle fibres (Figs. 16 and 17).

Phagocytosis of sarcous substance, so prominent a feature of essential myositis,[10] was not seen in any case. It may occur in late cases of dermatomyositis.[7] Syncytial cells seen in attempted regeneration of muscle were not a feature.

VASCULITIS

Reaction of blood vessels was identified at all levels of the vascular tree from small arteries to small veins. A single example of the focal lesion of polyarteritis nodosa in a medium muscular artery was seen in Case 1. But mainly the lesions were proliferative, involving the endothelium or the thickness of the vessel wall or as a cuff of relatively undifferentiated mesenchymal cells around the vessel (Figs. 7-12). These vascular changes were conspicuous in vessels of medium size. However, with saline-Gram, vascular damage was seen to be much more extensive. Thus on examining the "fibrinoid" along the connective tissue planes one would frequently encounter a small mass shaped like a fibrin plug in a small vessel, and it would appear that in the acute fibrinoid necrosis of collagen of severe degree the small vessels are plugged with fibrin and their walls disintegrate and merge with the general debris. In addition, fine fibrinous infiltration of vessel walls was demonstrated by this method. In some vessels the wall was thickened by swollen altered collagen.

MESENCHYMAL REACTION AND CELLULAR EMIGRATION

Proliferation of mesenchymal cells as opposed to degeneration of connective tissue is also a feature of the collagen diseases, and is sometimes conspicuous and may be dissociated from purely degenerative reactions. Considering the degree of degeneration of collagen and necrosis of muscle in general, paucity of cellular response of the mesenchyme was a conspicuous feature of all cases except Case 8 (second admission). In general, there was increase of interstitial cells, but this could be absent and was always slight, apart from occasional perivascular cuffs. Occasional foci of small round cell infiltration were present in damaged muscle and in connective tissue. While cellular infiltration is the most frequently illustrated change in accounts of dermatomyositis, this is in part accounted for by a general failure to describe the specific changes, and hence these are the changes noted by the observers. Characteristically in our cases the sickness was a general one of the collagen, and of the fertile mesenchyme, which is usually so responsive to damage.

There was either scanty or no evidence of emigration of leukocytes and monocytes from the blood.

CHANGES IN THE SKIN

The biopsies were not taken in reference to skin rashes, and the cutis showed generally no change apart from occasional œdema and congestion. Damage was concentrated in the deeper layer of the dermis and the panniculus as congestion of vessels, œdema, fine fibrinous infiltration of interstitial planes, increase in interstitial nuclei and fibrinoid necrosis. The latter

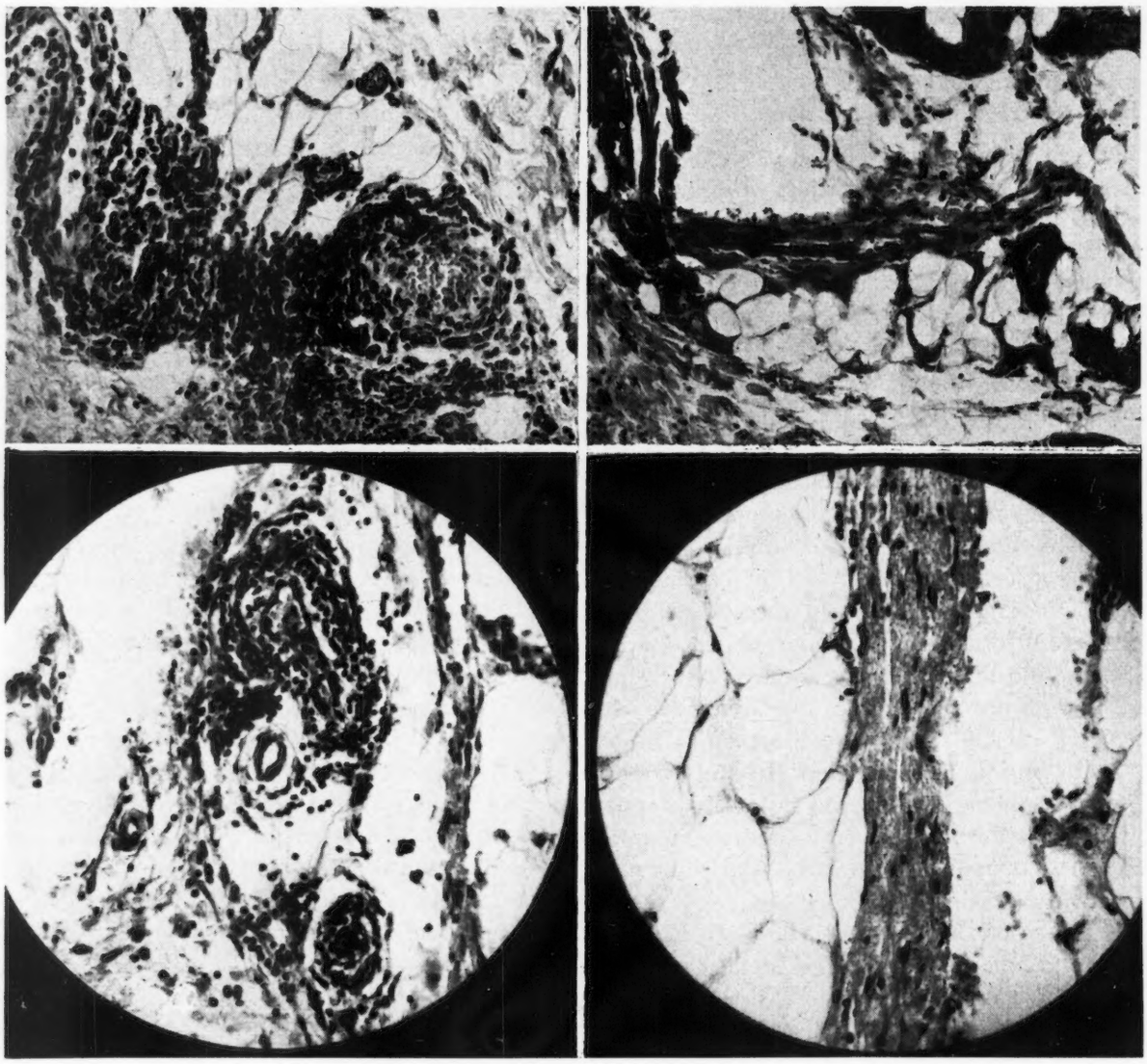


Fig. 19 (Case 8, second admission).—Small vessels in the panniculus obscured by round-cell infiltration (Hæmatoxylin and Eosin). **Fig. 20** (Case 8, second admission).—A small vessel, cut longitudinally, illustrating swelling of endothelial cells and wall (Hæmatoxylin and Eosin). **Fig. 21** (Case 4).—The endothelium of small vessels is swollen, and the nuclei are pyknotic; there is perivasculitis. A connective tissue septum of the panniculus is swollen and granular (Hæmatoxylin and Eosin). **Fig. 22** (Case 4).—Shows the characteristics of granular disintegration of collagen (Hæmatoxylin and Eosin).

was demonstrated as granular disintegration of fine collagen fibres or occasionally as swollen fibrinous insertions in the course of a collagen fibre (Figs. 21 and 22). In three of the acute cases fascia showed marked fibrinoid necrosis. Vasculitis was also present but relatively inconspicuous except in occasional veins.

In Case 7, nodules were noted clinically in the panniculus. These showed vascular congestion, perivasculitis and fibrinoid degeneration of vessels, proliferation and necrosis of fat cells. The appearances were similar to the nodules of Weber-Christian disease. In Case 8 (second admission) the deep dermis in the areas of erythema and induration showed intense change—œdema, congestion, generalized perivasculitis, focal obliteration of small vessels by proliferation or fibrinoid necrosis, interstitial proliferation of mesenchymal cells, mast cells, granular œdema, and fibrin infiltration of collagen. That is to say, a conspicuous degree of nodular vasculitis similar to many drug reactions. Focal accumulations of eosinophil leukocytes were also present; this was not noted in all the other cases. The adjacent muscle showed fibrinoid necrosis of collagen and perivasculitis (Figs. 19 and 20).

Comment.—Cases 4 and 7 call for further comment; the remainder had a classical clinical and pathological picture.

Case 4 might be taken as a drug reaction since a persistent and generalized rash of the face developed during treatment of stomatitis with sulfonamides. Awkwardness in walking was noted; there was no œdema. Slight vasculitis and fibrinoid necrosis were demonstrated in the deep dermis of the calf, and a patch of definite hyalin necrosis was noted in the middle of the wedge of muscle, free from any ambiguity in relation to the trauma of removal. The child got well rapidly. If we look upon it as an acute and evanescent allergic reaction, then at our present state of knowledge, we should look on classical dermatomyositis as a chronic allergy.

Case 7, the only permanent chronic case, showed throughout the muscle wedge a regular pattern of interstitial fibrosis. The muscle fibres were hypertrophied and abutting on the fibrous septa; the muscle cells were undergoing a slow lysis and collapse (Fig. 17). Hyalinization of connective tissue was more conspicuous than fibrinoid degeneration. Evidence of active disease in the form of small patches of hyalin necrosis of muscle was also present. There can be no doubt that this smouldering "rheumatism" of muscle is the disease referred to as myositis fibrosa in textbooks of pædiatrics, and first described by Batten in 1904.[11]

Cases 7 and 8 (second admission) did not show clinical œdema, but they had subcutaneous nodules. It would appear that the noxious mechanism, which in other cases led to brawny œdema, was in these cases more localized and more intense.

DISCUSSION

Early diagnosis of dermatomyositis. — The Boston workers emphasize that muscular weakness is the only constant clinical finding in the condition and biopsy of muscle the only method of definitely identifying the disease. Considering together the clinical findings and the pathology of the muscles in our cases, it would appear that muscular weakness is not marked until there is grave damage to muscle. Weakness is a common symptom of many diseases, and it is probable that muscle biopsy in children showing rashes and periorbital œdema will be a more practical counsel in obtaining early diagnosis.

The pathology of early lesions may not be discernible from that of an acute allergic reaction (*vide infra*).

Where possible, small biopsies should be avoided, and specimens should be taken with a minimum of trauma, as trauma to living muscle and collagen, and escape of serum into the tissues, provide appearances simulating dermatomyositis. In obvious examples of the disease the triad of vasculitis and degeneration of muscle and of connective tissue will be easily demonstrated in sections processed by the routine method for biopsies, but for more critical study of questionable cases slower methods are necessary.

Incidence.—Dermatomyositis is generally held to be a rare condition. The following facts cast some doubt on this. (1) Our study demonstrates that children with very severe lesions can be restored to normal health, and therefore minor cases probably recover frequently without special attention. (2) Biopsy is the only way to positively identify the disease, but many communications deny a specific pathology. In diagnosis by biopsy there must be much confusion from not recognizing fibrinoid necrosis as the hallmark of the disease. (3) Textbooks in general make little reference to the disease, and generally paint a horrific picture of remorseless progression to contracted ulcerated limbs, which is erroneous. Accordingly, the disease is probably more common than is generally recognized.

Action of cortisone.—While our study has thrown no new light on the etiology of the disease, in the acute condition in children there was a remarkable paucity of cellular response on the part of the mesenchyme, and in our cases we would regard this as a feature just as outstanding as vasculitis and degeneration of connective tissue and muscle. In the acute collagen diseases treated with cortisone we have only recognized dramatic and lasting response in cases of polyarteritis nodosa and nodular vasculitis associated with a marked and healthy cellular response. It may be that future studies will prove this to be a guide to the response to cortisone. Acute rheumatic carditis is also characterized by a paucity of cellular response and does not respond to cortisone.

Fibrin and "fibrinoid".—Fibrinoid necrosis of connective tissue is recognized as the hallmark of the collagen diseases. There is no agreement as to its nature. Fibrinoid necrosis of connective tissue associated with vasculitis is encountered also in tissues damaged by irradiation and in nodular vasculitis. Nodular vasculitis comprises a group of conditions variously described clinically as nodular vasculitis, papulo-necrotic tuber-

culide, erythema nodosum, erythema induratum, localized scleroderma, Weber-Christian disease, and drug rashes. The combination of fibrinoid necrosis and variable vascular lesions encountered in dermatomyositis is similar to the range of lesions encountered in the group of nodular vasculitis. It is noteworthy that individual conditions coming under this heading are manifestly allergic reactions or no etiology is determined. This is the morphological basis for the belief that dermatomyositis is essentially an allergic disease.

In addition to the above conditions, swollen anuclear collagen giving a range of routine staining reactions from fibrin to hyalin is encountered in the base of gastric ulcers and in the stroma of tumours, particularly relatively simple tumours with a poor blood supply.

While this communication is not concerned with a histochemical analysis of fibrinoid necrosis, considering our observations on all of the above conditions, we believe that in acute fibrinoid necrosis, as seen in the acute collagen diseases and in allergic lesions, two processes are involved. The acute reaction appears to be essentially proteolytic. As the collagen fibres are broken down, there is an escape of fibrin from the blood, so that the disintegrating products are bound together. Later the fused mass, consisting largely of fibrin if degeneration has been gross, undergoes a metamorphosis to a temporary connective tissue, a hyalin. Reticulin fibres, the constituent fibrils of collagen, are eventually laid down in the hyalin matrix. Thus, the fibrin infiltration is an adaptive mechanism to provide a temporary connective tissue. Without such an assumption we cannot see how such gravely ill children with so grave a disruption of their collagen could make such a remarkable recovery. It is noteworthy also that no evidence of absorption of "fibrinoid" by cellular mechanisms was seen. Some analysts deny the presence of fibrin in "fibrinoid". This is to deny that the damaged vessels in irradiation lesions, in allergic lesions, and in acute collagen diseases are not leaking fibrin. A similar explanation of fibrin metamorphosis can explain the "fibrinoid" in chronic ulcers, in the walls of bursæ, and in tumours with an unstable vasculature.

General Morphology

We do not need to labour the point that the disease is characterized by the triad of vasculitis, fibrinoid necrosis of connective tissue, and degeneration of muscle. Hyalin necrosis of muscle is not specific for the disease. The sarcolytic degeneration which was conspicuous has not been seen by us in other diseases of muscle. Skin lesions are deep in the dermis, and in the panniculus. Since the wide range of vasculitis and the fibrinoid necrosis encountered has a parallel morphology with allergic reactions in general, it is convenient to regard dermatomyositis as essentially an anaphylactoid reaction in which the noxious mechanism is more continuous than in acute reactions and prevents cellular reaction. The findings agree well with Gladstone's[12] account of the mechanism of anaphylactoid reactions: a surface reaction liberating histamine and heparin, and probably involving proteolysis. In dermatomyositis proteolysis is conspicuous (lysis of collagen), basement membranes (mucopolysaccharide) are spared, and despite gross damage to vessels there is often a general absence of thrombosis indicating a thrombolytic mechanism. Dermatomyositis is a poor name. Rheumatic myositis and panniculitis would be more explanatory.

Summary

A description is given of eight cases of dermatomyositis in children. Two children died, and one girl is a cripple. The remainder recovered completely, including one patient who had a relapse. The disease is characterized by muscular weakness, rashes and brawny œdema, or subcutaneous nodules. Orbital œdema and rashes about the face are common.

Biopsy of skin and muscle exhibited degeneration of muscle, vasculitis, and, to a conspicuous degree, fibrinoid necrosis of connective tissue. There was also a paucity of cellular response in the damaged tissues except in the nodular lesions of the skin. Lesions in the skin were deep. In addition to hyalin necrosis of muscle, sarcolysis was an outstanding feature.

The study showed that children with severe lesions can be restored to full health.

Reasons are given for believing that the disease is commoner than is generally assumed.

The morphological correlation between allergic lesions and dermatomyositis is briefly referred to.

It is emphasized that fibrinoid necrosis of connective tissue is not a single reaction, and because of the rapid recovery from gross lesions

it is considered that an adaptive mechanism to bring about repair must be inherent in it. It is considered that fibrin plays an important part in this mechanism.

The staining methods used will be published in a separate communication.

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RÉSUMÉ

La triade symptomatologique sur laquelle est fondé le diagnostic de dermatomyosite, à savoir dégénerescence du muscle, dégénerescence du collagène et vascularite, date de 1921 (Fahr). Les autres se sont proposés ici de reprendre le problème à la lumière des données recueillies à l'étude de 8 cas vus à l'hôpital des enfants de Halifax (N.E.). Le diagnostic fut confirmé dans chaque cas par une biopsie. L'affection s'est présentée dans la majorité des cas par une stomatite ou une pharyngite, avec érythème de distribution variable d'un début insidieux et intéressant surtout les extenseurs. On a noté aussi un œdème induré ne prenant pas le godet, sorte d'épaississement de la peau, survenant aux régions frontale périorbitaires, articulaires, quelquefois asymétrique ou généralisé. Tous les petits malades (prédominance de filles sur les garçons) se sont plaint de douleurs et de sensibilité diffuses, et ont accusé une fièvre habituellement de faible intensité à une étape quelconque de la maladie. L'adénopathie lymphatique de peu d'envergure bien que présente dans quelques cas se perdit dans l'abondance des autres signes. On ne trouva de leucocytose ou d'éosinophilie en aucun cas, ni aucune anémie de quelque importance. Certains de ces enfants reçurent différents antibiotiques lorsque l'on jugea bon de leur en administrer, cependant les guérisons spontanées rendirent l'interprétation des résultats thérapeutiques très douteux. En plus de ces cas où la maladie disparut d'elle-même sans laisser de reliquat, on a noté une récidive après trois ans, entraînant une paralysie de certains groupes de muscles et la calcification des tissus mous surtout dans les jambes, et deux mortalités au cours de la phase aiguë. La maladie pourrait bien être plus répandue qu'on est porté à le croire.

Les descriptions histopathologiques détaillées des tissus prélevés au cours des biopsies sont données dans le texte. Il est intéressant de remarquer que la vascularite s'étendait aux vaisseaux de tous les calibres, des petites artères aux petites veines, sans cependant donner lieu à des phénomènes thrombotiques. La sarcolyse observée en maintes occasions serait aux yeux des auteurs un phenomène remarquable dont l'importance diagnostique gagnerait à être mise en évidence. L'indolence de la réaction cellulaire mésenchymateuse est si caractéristique qu'elle devrait être incluse dans la triade diagnostique mentionnée plus haut. Cette pénurie de la réaction cellulaire pourrait expliquer par analogie l'inefficacité de la cortisone puisque les cas de périartérite noueuse où ce médicament n'apporte aucune amélioration sont précisément ceux où cette réaction fait défaut. La faiblesse ne peut être considérée comme un symptôme précoce puisque'elle ne se manifeste qu'après une dégénérescence musculaire avancée; les auteurs recommandent plutôt le recours plus fréquent à la biopsie. On doit la pratiquer avec une grande délicatesse dans la manipulation des tissus puisque les traumatismes peuvent donner lieu à des altérations simulant les lésions que l'on retrouve dans la dermatomyosite. Se basant sur les ressemblances histologiques entre les vascularites noueuses d'origine allergique et la dermatomyosite les auteurs prétendent qu'elle ne serait qu'une réaction anaphylactoïde dont le mécanisme nocif persisterait plus longuement que dans les formes aiguës, et empêcherait la réaction cellulaire.

NOTES ON NEONATAL THRUSH AND ITS EPIDEMIOLOGY*

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ORAL CANDIDIASIS or thrush in the newborn infant remains a significant problem in hospital nurseries. The factors underlying its occurrence and spread need further investigation, and occasional notes on its epidemiology seem appropriate.

The widespread occurrence of *Candida albicans* in the normal flora of humans has led to the belief that infections due to it are of endogenous origin. It is considered, furthermore, that the micro-organism is essentially an "opportunist", causing infection only secondary to definite predisposing factors such as general or local debility of tissues following other disease or trauma. A disturbance in the normal bacterial flora of a particular area of the body resulting from antibiotic therapy is thought to be another predisposing factor.

The problem in newborn nurseries often presents complexities which make complete acceptance of these views difficult. On occasion, infants develop thrush when predisposing factors are not apparent unless early age is accepted as one such factor. Epidemic outbreaks of oral

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candidiasis occur, suggesting an exogenous rather than an endogenous source. Even the most careful nursing techniques usually fail to eliminate thrush altogether though they may reduce its incidence considerably. This suggests an endogenous source of infection, particularly if the term "endogenous" includes the baby and the mother as a single unit. The intermingling of the two processes of cross-infection and endogenous infection often makes it difficult to recognize the true situation within a nursery and to take appropriate measures for control.

PRESENT STUDY

This study was undertaken to investigate the incidence of *C. albicans* in the vaginas of parturient women and of thrush in the infants born of these mothers and the source of infection in all babies in the nursery. It was done in the wards of a general hospital where facilities of staff and equipment were such that cross-infection was believed to play little part in the sporadically occurring cases of thrush. The nursery contained 92 cots, each in a small, separate, open cubicle, and a further isolation unit of nine cots for infected cases.

The investigation included all women who were delivered on the public service of the hospital during the three-month period of October, November and December. Cultures were taken from the post-partum vaginal discharges of all mothers and from the mouths of their offspring. These were taken on one occasion early in the first week following delivery except in one infant from whom oral cultures were obtained only on the 13th day.

The swabs were plated directly on both Bacto-Sabouraud maltose agar and Bacto-chlamydospore agar. The primary cultures were incubated at room temperature for four days, and strains of Candida were replated on blood agar to ensure pure cultures. The identity of each strain was determined by its ability to produce chlamydospores on corn meal agar, Bacto-chlamydospore agar and sheep blood agar, and by its fermentation reactions on dextrose, maltose, sucrose and lactose.

The sensitivity of each strain to nystatin* was determined, using serial doubling dilutions of the drug in Bacto-penassay broth in volumes of 5 ml. The primary standard solution of nystatin was made by dissolving 100,000 units in 2 ml. of propylene glycol. The inoculum in each tube was a standard loopful of an 18-hour broth culture. Readings were taken after incubation for five days at room temperature; controls indicated that propylene glycol in the concentrations present in the tubes did not interfere with growth.

There were 127 mothers in the series. These gave birth to 132 infants, of whom four died. All five pairs of twins survived. In all, 128 infants were followed up.

Candida species were isolated from the vaginal discharges of 19 mothers. One strain proved to be *Candida tropicalis* and one was *Candida krusei*. The remaining 17 were *Candida albicans*, an incidence of 13.4% in these mothers. The reported frequencies of the organism in vaginal cultures have varied from 5% to 47%.[1-5] Its incidence is high during pregnancy and in women showing clinical evidence of vaginitis, but asymptomatic carriers have been noted by most workers. None of the present series had symptoms of vaginitis.

C. albicans was found early in the mouths of six infants, an incidence of 4.7%; *C. tropicalis* and *C. krusei* were not isolated from any infant. All six babies were born of mothers yielding positive vaginal cultures and it seemed likely that infection occurred from the birth canal during delivery. Such contamination was not detected in 13 infants whose mothers showed positive cultures, and *C. albicans* was not found at any time in newborns from mothers whose cultures were negative, except for the two instances noted below.

All of the six infants with positive cultures developed clinical thrush. This became evident on the fourth day in one child, on the sixth day in two, on the seventh in one and on the eighth day in two. Five were breast fed; one received artificial feedings only. A seventh infant from a mother with a positive culture also became infected. This baby was delivered by Cæsarean section. The early mouth cultures were negative, yet thrush developed on the 12th day. This infant was breast fed, and it is probable that it acquired *C. albicans* from the mother during the times of feeding. Twelve infants from mothers whose cultures were positive appeared not to have been contaminated and escaped thrush. Five received artificial feedings and seven were breast fed.

*We are grateful to E. R. Squibb & Sons for a supply of standard "Mycostatin" (nystatin) powder.

Clinical candidiasis occurred in only two other infants of the series of 128. Both were from mothers with negative cultures and were breast fed. In both the disease was recognized on the sixth day. False negative cultures may have been obtained from the mothers or the babies. The source of infection was inapparent in one, but the second may have acquired the micro-organism from the first, who occupied an adjacent cubicle.

No other cases of thrush were reported in the entire nursery during the period of study, and no infants other than those studied were transferred for this condition to the special isolation cubicles. The apparent absence of candidiasis in all infants in the nursery not included in this survey may not be a reliable observation because it was customary to send infants of mothers in semi-private or private rooms home on or about the fifth day under the care of a pædiatrician, whereas public ward babies were kept usually for seven days.

A clinical history of past vaginal infection in the mothers with positive cultures was not elicited. Predisposing factors in the infants were not apparent. Of the 128 live babies, one had a cleft palate, one had a spina bifida and six were premature. None of these developed thrush; all cases were among the normal newborns.

The identification of *C. albicans* presented some difficulties, particularly in assessing the production of chlamydospores. This has been noted by others.[6] A single attempt on a single medium, either corn meal agar or Bacto-chlamydospore agar, often failed to demonstrate these structures. However, with repeated tests on several media, the production of chlamydospores became obvious. This feature, together with growth characteristics and the ability to ferment glucose, maltose, sucrose and not lactose, made differentiation and identification possible. No differences were detectable between those strains producing and those not producing clinical infection.

All strains were about equally susceptible to nystatin, including *C. tropicalis* and *C. krusei*. The minimal inhibitory concentration was 8 units per ml. for 14, and 4 units per ml. for the remaining 15 strains. Subcultures from the tubes containing fully inhibitory concentrations of nystatin failed to grow, suggesting a bactericidal activity under the conditions of the test.

DISCUSSION

This study does no more than confirm the observations of others that *C. albicans* in the vaginal flora of the parturient mother is an important factor in the development of thrush in her newborn infant.

Almost all investigators have reported good correlation between the presence of *C. albicans* in the mother and the occurrence of thrush in the infant. Woodruff and Hesseltine[7] estimate that the baby has a 35-times greater chance of developing the disease if the mother harbours the organism. Ludlam and Henderson[3] on the other hand did not find a significant relationship to exist, but this might have been obscured by the other contributory factors that they investigated. Secondary cases of thrush may arise from cross-infection within a nursery resulting from contacts with personnel, unsterile artificial feedings, fomites, etc., but control of these factors cannot prevent the disease in those infants acquiring the infection from their mothers.

In our series of 128 infants, there were nine who developed thrush. Two cases probably were related to cross-infection, but the remaining seven babies acquired the infection primarily from their mothers.

Contamination of the infant by the mother might occur at the time of delivery or during the post-partum contacts. In only one of our seven primary cases was there reason to believe that the organism was not acquired from the birth canal. The ease with which infection can be induced by the experimental inoculation of cultures into the vagina of adults or into the mouth of infants has been demonstrated by several workers.[8, 9] All of six infants with positive cultures in our series developed clinical thrush, and only 12 viable infants from mothers with positive cultures escaped contamination or did not develop the disease. Not only has the organism high pathogenicity for the young, but predisposing factors seemed unimportant in our series as in those of others.

The complete control of candidiasis in nurseries requires more than attention to the details of nursing techniques on the wards. The primary cases are the potential sources of danger, and these are the infants of mothers who harbour *C. albicans*. Ante-partum vaginal cultures might be taken from all women during pregnancy, and the separation of all babies from the mothers with positive cultures together with

their isolation on the ward until they are shown to be free of the infecting organism might be considered. Such separation, however, is undesirable for many reasons, and a better approach to the problem might be in prophylactic measures directed at the infant or at the infected mother. Of the anti-candidial agents known, nystatin appears to be the most suitable for this purpose. It is effective clinically,[10-13] and seems capable at times of eradicating the organism.[12] This latter is in accord with our *in vitro* observations, though our experience in treating thrush has been that the topical application of nystatin, while usually effective clinically, often only reduces the numbers of Candida to a very low level. The drug might be applied as a routine vaginal prophylactic to pregnant women during the immediate ante-partum period, or such use might be reserved for those with positive cultures.

Its application prophylactically to those infants born of women with positive cultures would seem to be a reasonable approach to the problem. This might prevent not only thrush in the baby but also the spread of the infection on the ward.

SUMMARY

1. *Candida albicans* was found in the vaginal cultures taken during the early post-partum period in 13.4% of 127 women.

2. *Candida albicans* was found in oral cultures taken during the early neonatal period in 4.7% of 128 viable infants. All babies with positive oral cultures were born of mothers with positive vaginal cultures. It was believed that contamination occurred from the birth canal during delivery.

3. All contaminated infants developed thrush.

4. Only three non-contaminated newborns developed thrush; one was related to post-partum contacts with the infected mother, and two may have been due to cross-infection.

5. The epidemiology and control of thrush in nurseries is discussed.

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RÉSUMÉ

L'origine du muguet est probablement endogène si l'on veut bien englober en un tout la mère et l'enfant. Les auteurs ont fait des cultures du vagin des accouchées et de la bouche des nouveaux-nés afin d'isoler le *monilia albicans*. On le retrouva chez 13.4% des mères et 4.7% des enfants. Tous les enfants infectés étaient nés de mères porteuses du germe. (Deux autres genres de Monilia furent aussi isolés.) Tout porte à croire que l'infection de l'enfant s'acquiert dans le vagin de la mère pendant l'accouchement, ou dans la période qui le suit immédiatement. L'emploi de nystatin lorsqu'indiqué semblerait la meilleure mesure prophylactique.

DIAGNOSTIC ENDOSCOPIC PROCEDURES*

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IT IS OF INTEREST, and usually of value, to pause occasionally and review the progress that has been made in some particular field of medicine or surgery with the passage of time. There is no field in which such research is more rewarding than in that of endoscopy. This specialty has developed rapidly as the result of the ingenious devices of men's minds and hands, and in company with the expansion of medicine and surgery. In particular, endoscopy of necessity paced the rapid development of chest surgery, because of which the accurate description of an œsophageal or bronchial lesion becomes of great practical significance.

As early as the beginning of the nineteenth century, physicians began to explore the con-

*From the Department of Otolaryngology, University of Toronto. Presented at the Annual Meeting of the Canadian Otolaryngological Society, Bigwin Inn, Ontario, June 17, 1955.

tinuations of the pharynx, using the reflections of various types of illumination to light the way. It was this problem of illumination which restricted further development in the field, until Edison, in 1879, invented the carbon incandescent lamp and opened a new era for endoscopy.

During the next 20 years, many new instruments were devised by Nitze, Mikulicz, Killian and others. Killian, in 1897, was the first to carry out a bronchoscopy for the removal of a foreign body from the left main bronchus. His instrument was an 8-mm. œsophagoscope 25 cm. long, which, in comparison with our instruments today, was rough indeed. Nevertheless, he demonstrated the possibility of examining the upper respiratory tract under local anæsthesia using rigid tubes. It of course remained for Chevalier Jackson, on this continent at least, to combine the knowledge of the previous hundred years and perfect tools and methods by which the bronchial tree, œsophagus and stomach might be directly examined. In England great contributions have also come in recent years from Sir Victor Negus.

In its early stages, endoscopy concerned itself with the problems of instrumentation and technique, chiefly for the purpose of the removal of foreign bodies from the food and air passages. Certainly such procedures required—and still require—the utmost in skill and co-operation by all those associated with such a case, and the developments in physical fields have been adapted to the problems involved. Nevertheless, the growth and significant development in this particular field has been in other directions in the past few years. Endoscopy is a dynamic and constantly changing interest. The bronchoscopist soon becomes aware of the great variety of inflammatory, obstructive and neoplastic lesions which he can see and handle, and which require an extension of his interest in the field of pathology, medicine and surgery, with special reference to the chest. In order that he may make his maximum contribution, he must be as familiar with the stethoscope as with the laryngeal mirror, and as conversant with the radiographic evidence of disease in the lung as in the accessory nasal sinuses. Moreover, it is necessary for him to keep abreast of the developments in these fields and to contribute to such advances and meet new needs as they become apparent. Recently, for example, pulmonary surgeons have been exploring the possibility of resection of areas of bronchial stenosis, with a view to the salvage of large sections of normal pulmonary tissue which must otherwise be sacrificed. This requires the development of a new technique of pulmonary grafting. Certainly, in this particular field, there is only one way in which the extent, degree and condition of the strictures can be determined preoperatively, and that is via the bronchoscope. Furthermore, the postoperative care is once more the function of the endoscopist.

It is equally important that the œsophagoscopist be an authority in the diseases of the structure with which he deals. He must be thoroughly familiar, also, with the surgical and medical techniques in dealing with this structure and the recent advances in that field. The œsophagus, far more delicate than the bronchus, demands a delicacy of touch which cannot be developed except by constant practice and perfection of technique. The penalties of neglect can be most severe indeed, even in these days of chemotherapeutics. Despite this perfection of technique, there still remains a considerable field of of endeavour. A surgeon may now directly attack the œsophagus, and he requires certain definite information to allow him to assess the operability of the lesion with which he is going to deal. The œsophagoscopist must be familiar with the problems of the surgeon and his scope in order to anticipate the information necessary. He must also form part of the active team engaged in the handling of the patient. It is often possible, through the œsophagoscope, to pass a duodenal tube beyond the obstruction caused by tumour or stricture and thus turn a desperate case to one which can be maintained and properly prepared for surgery. There are many other examples of teamwork which will improve the patient's chances and in the long run further broaden the field of endoscopy. In the case, for example, of hiatal hernia with shortening of the œsophagus, œsophagitis and possibly stricture formation, the role of the endoscopist, surgeon and internist is forever changing and developing. In the early cases, perhaps, surgical excision is the treatment of choice if medical management is not sufficient. On the other hand, direct and indirect bouginage will control and prevent the development of stricture in late cases and allow the patient to live a normal life without surgery. Whatever the decision, it cannot be correctly

made unless one is able to visualize the area involved directly.

In order to pass an œsophagoscope or a gastroscope, it is necessary first to visualize and pass by the structures of the pharynx and hypopharynx. In order to pass a bronchoscope, the larynx must be seen and the cords separated. To attempt a bronchoscopy or œsophagoscopy without first visualizing these areas by indirect methods is to invite unnecessary difficulties and dangers. It is much easier to visualize a distorted larynx by mirror than through a scope, and by doing so an assessment of the difficulties may be accurately made. Such a precaution will save many a tracheotomy done as an emergency procedure. Diseases of the nose, throat and sinuses may have a profound effect upon the appearance and health of the larynx and hypopharynx, and the source of hæmorrhage, sought for most carefully in the lower bronchi or œsophagus, may be seen in the nasopharynx by a nasopharyngeal mirror. The endoscopist must be familiar with the examination, by all available means, of all the structures pertaining to and associated with his field.

Carcinoma of the œsophagus cannot be considered as a cancer seen at the end of a rigid tube, but as a variable disease affecting a living patient, whose whole course of treatment and future can be profoundly influenced by the results of the œsophagoscopic examination. A stenosis of the bronchus is not a nuisance because of its obstruction to the further passage of the bronchoscope, but is a physiological and pathological change in the bronchus which has far-reaching effects on the lung distal to it and in the patient as a whole. It may also have a story to tell of the disease process which has gone before. Thus the early emphasis on skill and technique has broadened and changed and developed, and so must the endoscopist develop with it.

One of the foremost endoscopists of today is Dr. Edward Benedict. In the foreword to his book, Dr. Edward Churchill, thoracic surgeon of Boston, says in summing up the secret of Benedict's success: "The subject matter of the area has been first and foremost the patient, and not merely the technical skill of taking a look at his insides." As Benedict himself says, "An endoscopist must see the patient as a whole. He must be much more than a passer of tubes and more than an interpreter of one small spot in the body at the end of a tube."

A further development in the field of endoscopy has been the drift of the science from the hands of otolaryngologists who developed it, into the hands of various other surgeons and internists. A chest surgeon and a chest physician and the pure endoscopist have in many places superseded those who originally developed the art. It is said: " The man who does the surgery should look down the bronchoscope." This is one of those statements which makes sense on the surface but will not stand up to close scrutiny. Such a man must be only an occasional endoscopist who sees a limited number of special cases. He cannot have the necessary practice to develop the technique and he has not the broad interest to contribute to the wider field. He must either become a surgeon and occasional endoscopist, or an endoscopist and occasional surgeon. The same must apply to the internist, and in neither case can adequate facilities for training others be set up. The endoscopist must be one who does sufficient examinations of all types to develop a meticulous technique and skill and who therefore has the material with which to teach. He must have a broad interest in and knowledge of the medical and surgical problems and capabilities in the regions he examines, and he must be able to keep up with the developments in these often widely diversified fields. He must also, perforce, have a knowledge of the diseases of the ear, nose and throat and be able to examine these in an expert manner. These qualifications and abilities lie squarely within the field of the otolaryngologist and it is up to him to demonstrate his complete competence in this field. It is reported that about 50% of all endoscopy is now done by the internist or thoracic surgeon. It is quite possible that this may increase but, while we are willing to make some concessions to the invasion of what was once our private preserve, we still feel strongly that we are the best fitted to do this work successfully.

ASSESSMENT OF OUR RESULTS

It was decided that as we were in the fortunate position of still retaining endoscopy in our Department we might attempt to assess our work. It would be impossible to give a complete report of the results in so short a time even if the survey were complete. It is proposed to ignore laryngoscopy entirely and only touch a few of

the highlights in œsophagoscopy. One of us (D.P.B.) and our resident, Dr. Goodman, have gone over 750 records at only one of the hospitals, out of a total of about 2800 cases in a two-year period (Table I). It is interesting to find where we have failed in our diagnostic procedures and where we have been of assistance.

TABLE I.—DIAGNOSTIC PROCEDURES DURING 2-YEAR PERIOD

	*University of Toronto Teaching Hospital No.**	*Toronto General Hospital No.**
Bronchoscopies	1512	378
Œsophagoscopies	753	199
Laryngoscopies	521	175
Total cases	2786	752

*Excluding many repeat examinations.

The indications for œsophagoscopy are presented in Table II.

TABLE II.—INDICATIONS FOR ŒSOPHAGOSCOPY

Foreign body	44		
Carcinoma	51		
Stricture	76	Simple stricture	34
		Hiatal hernia	34
		Cardiospasm	8
Insertion Souttar tube	6		
Other reasons	22		
Total cases	199		

There were three cases of mediastinitis complicating œsophagoscopy, with two deaths. One case was due to a hiatal hernia, one to upper third stricture, and one to dysphagia with no diagnosis. In no case was difficulty or complication expected.

As three cases of mediastinitis in 200 examinations seemed like a large figure, we extended our investigation to six years in order to be sure that this was a true analysis, and found only two additional cases, with one death. This would give an over-all mortality from this procedure of around ½% in all types of cases. In a hospital where the residents are doing this procedure in their training, this mortality does not seem unusually high.

TABLE III.—INDICATIONS FOR BRONCHOSCOPY

Carcinoma	114
Postoperative atelectasis	38
Tuberculosis	35
Chronic pulmonary infections	69
Hæmoptysis	21
Other causes	111
Total cases	378

The indications for bronchoscopy are given in Table III.

In order to shorten this presentation, the findings in carcinoma of the lung only will be discussed (Table IV). In this most important disease of the atomic and cigarette age, we wished to see if we were carrying our share of the most essential early diagnosis.

TABLE IV.—CARCINOMA OF THE LUNG

Cases thought positive on bronchoscopy	85 (74.5%)
Cases negative on bronchoscopy (proven)	29 (25.5%)
Total cases	114
	Cases
Positive bronchoscopic picture	85 (74.5%)
Positive by biopsy	54 (47.3%)
Positive by cytology, negative by biopsy (Aspiration 2, sputum 0)	2 (1.8%)

After perusal of the results by smear by Cromwell and Papanicolaou[1] of Cornell, Clerf, Herbut and Nealon of Jefferson,[2, 3] and Gregg, Merkel and Cross[4] of Iowa, we are almost ashamed to present our figures. Our percentage by direct tissue biopsy was quite reasonable in view of the inaccessibility of many of these lesions. In 72 cytological examinations of aspiration we found positive malignant cells in 22 cases, suspicious malignant cells in seven cases (40.3%), and negative malignant cells in 43 cases.

The recent report of 82.3% positive cases from Iowa has forced us to reconsider our position in this procedure. I have discussed with the Professor of Pathology and the hospital pathologist our poor figures. We are all convinced that a chain is only as strong as its weakest link and we must inspect all links. The specimens were formerly processed by a Division of the Ontario Cancer Foundation and screened there. They will now go to the Surgical Pathology Laboratory. A special Fellow in Pathology will follow the methods of collection to the examination as a research project. The Iowa method of scraping and "placer mining" the bronchial secretions will be adopted and the patient will be properly instructed about collection of sputum. We are all at fault, and whether smears or paraffin sections are made of the material, there is great hope for this diagnostic procedure.

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RÉSUMÉ

Les progrès de l'endoscopie sont allés de pair avec ceux de l'éclairage, et l'avènement de l'ampoule incandescente a apporté des améliorations importantes dans le fonctionnement des instruments. Parmi les grands noms à signaler dans ce domaine se trouvent ceux de Chevalier Jackson et de Victor Negus. Ne servant au début qu'à l'extraction des corps étrangers des voies respiratoires et digestives hautes, l'endoscopie a tôt assumé un rôle diagnostique qui a forcé les opérateurs, à qui on ne demandait d'abord que de la délicatesse et du doigté, à étendre leurs connaissances aux chapitres thoraciques de la médecine interne et de la radiologie. L'endoscopiste a maintenant à se prononcer sur l'apparence d'une lésion; il doit éviter l'erreur de ne considérer un cancer que comme un rétrécissement de la lumière d'un viscère, aperçu au bout d'un tube métallique. Il lui faut au contraire en saisir toute la portée au point de vue du malade. Le passage sous observation directe d'un tube dans une sténose œsophagienne néoplastique est souvent une mesure préopératoire d'importance capitale. L'auteur s'élève contre les aspirations des chirurgiens et des spécialistes en médecine interne, à faire de l'endoscopie. Ces interventions devraient rester du domaine de l'otorhinolaryngologie à cause de l'expérience qu'en ont les spécialistes en cette matière.

BLEEDING FROM THE OVARY: GRAAFIAN FOLLICLE AND CORPUS LUTEUM*

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THERE IS NO ORGAN in the body into which bleeding occurs more frequently than the ovary.[1] Such bleeding is a common phenomenon in the life cycle of the graafian follicle and its derivatives. Though normally confined to the ovary, it may occasionally be excessive and result in free peritoneal bleeding. The clinical picture which follows simulates acute appendicitis or ectopic pregnancy so closely that laparotomy is often performed.

Surgery could almost always be avoided if the diagnosis were known for sure, since this type of bleeding tends to stop of its own accord.

With a view to clarifying this problem in general, we undertook a study of recent cases at the Vancouver General Hospital.

INCIDENCE

Only 93 cases had been collected and reported by Morton up to 1932,[2] but since then several hundred have been added.[3, 4] Obviously the disease is much more common than was formerly suspected.

We had 34 cases proven by laparotomy within two years and an additional 20 cases where the suspicion was strong enough to merit hospitalization but on whom operation was not done. Only the 34 cases proven by laparotomy are considered in this analysis.

In Table I this incidence is compared with that in more familiar conditions—namely, acute appendicitis and ectopic pregnancy, in a similar age group. In our experience, acute appendicitis was only five times more common and ectopic pregnancy only twice as common—a startling incidence of disease indeed. Previous indications of the frequent occurrence of ovarian bleeding were made by McSweeney and Wood,[5] who reported it one-thirteenth as common as acute appendicitis, and by Pratt and Haynes,[6] who consider ovarian hæmorrhage responsible for 17% of abdominal emergencies in menstruating women.

TABLE I.—COMPARATIVE INCIDENCE FOR 1954

Ovarian hæmorrhage	19 cases
Acute appendicitis (age 13-40)	96 cases
Ectopic pregnancy	38 cases

PATHOGENESIS

The blood supply to the graafian follicle is derived from a wreath of blood vessels surrounding the primordial follicles in the theca interna, the so-called perigranulosal vascular wreath.[1, 7] By following the fate of this vascular apparatus during the natural development of the follicle in its various directions, the pathogenesis of the follicle hæmatoma, the corpus luteum hæmatoma, and bleeding into the peritoneal cavity from either of these, becomes clear.

Several follicles start development each month but most of them fall by the wayside by the process known as atresia folliculi. The vascular wreath of such atretic follicles is quite well developed; consequently, it may break, bleeding into the substance of the ovarian stroma (this is rare), or more commonly into the follicle itself

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to produce the commonly seen follicle hæmatoma. Because these are relatively small in size and deeply placed, they do not frequently break into the peritoneal cavity.

The "follicle of the month" which goes on and outstrips the others displays an even greater intensity of vascularization in its wreath, so that at the time of ovulation it is quite well developed. However, the vascularization is still confined to the theca at this time and consequently, at the time of ovulation, bleeding into the follicle does not characteristically occur. The concept that bleeding does not characteristically occur into the ovary or from it at the time of ovulation is being stressed by recent authors.[7, 8] Consequently, such terms as corpus hæmorrhagicum, used to connote such bleeding at this time and to imply that it is very usual, are now not being used.[7] We wish to emphasize this point because it would follow that intraperitoneal bleeding will occur *at this time* if it is going to occur at all, and, as we shall see later, this is not the case.

It is *after* ovulation that this vascular wreath undergoes its really dramatic change. The vessels begin now to increase in size and number and to invade the granulosa cells, transforming them into granulosa lutein cells. They reach the lumen of the follicle about three days after ovulation whence a limited degree of bleeding may occur, usually of a zonal type, a layer of blood being adjacent to the lumen. More extensive vascularization at this time may lead to free bleeding and the formation of a corpus luteum hæmatoma or, when still more excessive, may burst and bleed freely into the peritoneal cavity.

Rather intense vascularization continues during the corpus luteum regression phase. It therefore follows that the predilection of such a corpus to bleed continues during its regression, indeed even over into the next cycle. In a significant number of our cases, a hæmorrhage proven by biopsy to be from a corpus luteum occurred within the first few days of a cycle, and we believe this to be bleeding from the regressing corpus luteum that belonged to the previous menstrual cycle. The following case is an example.

Mrs. E., aged 41 years, developed lower abdominal pain, nausea, faintness and pain on defæcation four days after the beginning of her last menstrual period. Abdominal examination revealed tenderness suprapubically and in the right lower quadrant, marked over McBurney's area with rebound tenderness to this side. No pelvic examination was done. The white cell count was 14,800 with a shift to the left. The preoperative diagnosis: "*Mittelschmerz* is ruled out on account of this occurring so shortly after the menses—acute appendicitis." Laparotomy revealed a considerable quantity of blood in the abdomen, the source of bleeding being the right ovary. Biopsy revealed, on microscopic examination, an *organizing* corpus luteum. We believe that this was a corpus luteum of the previous month's cycle bleeding during its period of regression.

Free bleeding tends to occur particularly after ovulation, and this predilection continues into the period of regression. This concept conforms with the more recent studies which report a preponderance of corpora lutea as the source of such ovarian hæmorrhage.[2, 4, 5, 9-12] Earlier studies attributed a higher percentage to bleeding follicles because of the timing during the menstrual cycle of the occurrence.[13-15] Whenever biopsies are secured, however, the bleeding is invariably reported to come from a corpus luteum.[10, 11, 14] All 20 of our biopsies were reported to show lutein tissue. Bleeding from a corpus luteum can occur at any time in a menstrual cycle.

Analysis of Material

This study is based on 34 operated cases. An additional 20 cases which were hospitalized but not operated on are not included. Material for biopsy was secured from 20 cases.

History

The usual story was of a sudden onset of lower abdominal pain, predominantly right-sided either at the beginning or soon after its onset. It commonly followed such activities as swimming, coitus, or sudden movement. Nausea and/or vomiting (usually nausea alone) was associated in about one-third of cases. Pain is most intense at its onset and seems to subside afterwards, in this respect differing from appendicitis.

More severe degrees of bleeding tend to simulate ectopic pregnancy except that the previous period is invariably normal. Thus, there may be faintness, shoulder pain, or pain on defæcation or urination.

On physical examination, there is commonly tenderness and guarding of the lower abdomen, most commonly on the right side. Similarly, rectal or pelvic examinations reveal tenderness on motion of the cervix and on palpation into the cul-de-sac.

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AGE DISTRIBUTION AND PARITY

The disease tends to occur in young women of low parity; 68% of all our patients were under the age of 30 (Tables II and III). Previous reports reveal an even higher percentage of young women.[3, 9]

TABLE II.—AGE DISTRIBUTION—34 CASES

Age	*No.*	*%*
Under 20	10	30
20 - 30	13	38
Over 30	11	32

TABLE III.—PARITY—34 CASES

Para	*No.*	*%*
0	19	56
1	8	23
Over 1	4	12
Not stated	3	9

Of our patients 79% were either primiparas or nulliparas.

LEUKOCYTOSIS (Table IV)

The white cell count is usually elevated and with a shift to the left. In 23% of cases, the white cell count was over 25,000 (Table IV).

TABLE IV.—WHITE CELL COUNTS IN 34 OPERATED CASES

White cell count	*No.*	*%*
Less than 10,000	10	30
10,000 - 12,000	3	9
12,000 - 15,000	9	26
Over 15,000	8	23
Not done	4	12

SITE OF BLEEDING

It is interesting that regardless of which ovary is involved, the pain is usually right-sided (Table V). In the first place, a larger number of right ovaries seem to be involved. This of course may be because a right-sided surgical condition in the abdomen draws more attention than one on the left side, and therefore these would be discovered more often. Yet even when the 12 left-sided ovarian hæmorrhages are considered, it will be seen that the majority led to right-sided tenderness. This experience is also reported by McSweeney and Wood.[5] It has also been observed to occur in bleeding ectopic gestations. We believe that this predominance of right-sided manifestations is due to the fact that when the cul-de-sac fills with blood, any overflow will tend to be displaced to the right side by the sigmoid colon.

TABLE V.—RELATIONSHIP OF OVARY INVOLVED TO SIDE OF PAIN—34 CASES

	Right ovary 20 cases	*Left ovary 12 cases*	*Not stated 2 cases*
Right pain	20	7	2
Left pain	0	5	0

TIME OF OCCURRENCE IN THE MENSTRUAL CYCLE

The fact that in 26% of our operated cases the last menstrual period was not even enquired after indicates how infrequently ovarian hæmorrhage must be suspected (Tables VI and VII).

TABLE VI.—ONSET OF SYMPTOMS FROM LAST MENSTRUAL PERIOD—34 CASES

L.M.P.	*No.*	*%*
1 - 9	7	21
10 - 16	8	23
17 - 28	7	21
Over 29	3	9
Not stated	9	26

TABLE VII.—ONSET OF SYMPTOMS FROM LAST MENSTRUAL PERIOD—20 BIOPSIED CASES

L.M.P.	*No.*	*%*
1 - 9	5	25
10 - 16	4	20
17 - 18	5	25
Over 29	2	10
Not stated	4	20

It can be seen that bleeding from the ovary can occur at any time in the menstrual cycle, but with a preponderance of cases after ovulation.

It may occur during pregnancy,[10] as it did in two of our cases. In one of the latter, a resection of the corpus luteum was followed by abortion.

PREOPERATIVE DIAGNOSIS

In 74% of cases the preoperative diagnosis was acute appendicitis and in 20% it was ectopic pregnancy (Table VIII). Near-correct diagnosis was made in only 6% of cases.

TABLE VIII.—PREOPERATIVE DIAGNOSIS—34 CASES

Diagnosis	*No.*	*%*
Acute appendicitis	25	74
Ectopic pregnancy	7	20
Twisted cyst	1	3
Ruptured cyst	1	3

JUSTIFICATION FOR SURGERY—IN RETROSPECT

If the diagnosis were known for sure in advance, operation could be avoided in most cases. In Table IX we have attempted to analyze the need for surgery from this point of view. Only in those cases in which bleeding was extremely severe or continued was operation considered to be justified, as well as in those with incidental lesions requiring surgery. In retrospect, therefore, only 20% required surgery.

TABLE IX.—JUSTIFICATION FOR SURGERY IN RETROSPECT—34 CASES

Justified	*No.*	*%*
Yes	7	21
Perhaps	6	17
No	21	62

AVERAGE DURATION OF HOSPITAL OBSERVATION

We think it significant in this poor record that 76% of cases were observed for less than five hours (Table X). Such a minimal duration of observation is really no observation at all, since it takes about this amount of time to admit a patient and book her for the operating room. Certainly no one would argue for procrastination once the diagnosis of, say, acute appendicitis is made for certain, but it is believed that, with careful and periodic observation in *suspect* cases of acute appendicitis, this observation time could with benefit be somewhat prolonged.

TABLE X.—DURATION OF HOSPITAL OBSERVATION—34 OPERATED CASES

Duration—(hours)	*No.*	*%*
Less than 5	26	76
5 - 10	3	9
10 - 24	4	12
Over 24	1	3

DISCUSSION

Bleeding from the ovary is a common cause of abdominal pain in women. The diagnosis is often missed because its general incidence is not appreciated and the condition therefore is not suspected. Thus, the last menstrual period was not even recorded in 26% of our cases, and pelvic examination was omitted in a similar number.

Milder degrees of intermenstrual discomfort, due to activity of the uterus, tubes or ligaments, are even more frequent.[16] From a questionnaire sent to 104 women McSweeney and Wood[5] determined that one in six questioned had some mid-interval discomfort incidental to intermenstrual phenomena.

There seems to be a widespread mistaken understanding of the pathogenesis of bleeding from the ovary. The notion that bleeding from the ovary will occur at the time of ovulation if it is going to occur at all is wrong and misleading. In this connection too, the use of the word *Mittelschmerz*, which is so well learned and remembered by the student, has also helped to fix the time of its occurrence at ovulation exclusively. The standard list of nomenclature for disease and operations omits coding for hæmorrhage from a corpus luteum. It may be for this reason that a higher incidence is not obvious in some hospitals.

Bleeding from the ovary may occur from either a graafian follicle or a corpus luteum, much more commonly the latter, and may occur at any time in the menstrual cycle and even in pregnancy.

Because of the close simulation of acute appendicitis and ectopic pregnancy, these patients are operated on without very much observation. In ectopic pregnancy, observation is usually quite safe at least while in hospital. On the other hand, it is more difficult to advocate any degree of prolonged observation when a condition closely simulates acute appendicitis. Nevertheless, some extension of the time of observation seems merited, particularly if the patient is under close periodic observation.

In order that this advocacy of more prolonged observation should not be carried too far, it should be remembered that appendicitis and bleeding from the ovary may co-exist,[3, 10, 15, 17] as it did in two of our cases.

Finally, if bleeding from the graafian follicle or corpus luteum is severe and continuous, operation is justified and indicated. The point, however, is that most sources of such bleeding stop in the course of one or two days. There have been no recent reports of mortality since 1937 when Johnson collected seven fatal cases.[18] If operation is done, the ovary can almost always be salvaged; although it was removed in several of our patients, this was entirely unnecessary.

We believe that in situations where the diagnosis of an acute abdomen in young women is in doubt, a reasonable period of observation should be carried out with careful re-examination

at short intervals to guard against the possibility of appendicitis or ectopic gestation requiring surgery.

Modern specalized methods of diagnosis might be exploited with benefit. Colpotomy, culdoscopy or pelviscopy[19] would all be useful adjuncts in arriving at the correct diagnosis.

CONCLUSIONS

1. Bleeding from the ovary is a common cause of acute abdomen in young women.

2. The source of such bleeding is usually a corpus luteum and it may occur at any time in the menstrual cycle, including menstruation and pregnancy.

3. It tends to simulate acute appendicitis and ectopic pregnancy in that order of frequency.

4. Bleeding will subside in most cases without the need for operation. A higher index of suspicion, a more prolonged period of observation in doubtful cases of acute abdomen in young women, and the resort to diagnostic methods such as colpotomy with or without a viewing instrument would result in a higher percentage of correct diagnoses and the avoidance of unnecessary surgery.

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RÉSUMÉ

L'hémorragie ovarienne est souvent à l'origine d'un abdomen aigu chez les jeunes femmes. Elle provient habituellement d'un corps jaune, rarement d'un follicule de Graaf; elle peut se produire à n'importe quelle période du cycle menstruel y compris pendant les règles ou la grossess et non pas uniquement au temps de l'ovulation. On peut la confondre avec une appendicite aiguë ou une grossesse extra-utérine. La plupart du temps l'hémorragies s'arrête d'elle-même sans qu'on ait besoin d'intervenir. Un bon nombre d'opérations inutiles seraient évitées si le diagnostic était correctement posé plus souvent. Pour en arriver là, l'auteur recommande de conserver cette éventualité présente à l'esprit, de garder plus longtemps sous observation les jeunes femmes présentant un abdomen aigu et de recourir à la colpotomie avec ou sans pelviscopie.

CHYMOTRYPSIN AS A DEBRIDING AGENT

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THE CRYSTALLINE ENZYME TRYPSIN was isolated from beef pancreas in 1932, and in 1935 the enzyme chymotrypsin was crystallized from the same source. In 1951 trypsin was introduced as a topical debriding agent, utilizing its property of selectively digesting non-viable cells and tissues. Trypsin proved effective in this field, but its high cost, due to the small yields obtained from pancreas, has proved a deterrent to its use.

The enzyme chymotrypsin is isolated from the pancreas as a by-product of the preparation of trypsin. The two enzymes are similar in their properties and are active under the same environmental conditions. They differ mainly in the locus of their attack on the peptide bond. Reiser, Roettig and Curtis[1] stated that the lysis of fibrin by chymotrypsin is only 25% that of trypsin alone, but that mixtures of chymotrypsin and trypsin of equal enzymic activity exhibit potentiated lysis to the extent of 270% that of trypsin alone. These workers refer to units of enzymes and mixtures of equal enzymic activity without describing either unit or method of assay. We find that the relative activities of

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the enzymes vary with the substrate and the method of determination of enzymic activity. We made observations on the dissolution of fibrin by solutions of trypsin and chymotrypsin and a mixture of the two enzymes, mixed in equal parts by weight. The enzymes were lyophilized, salt-free preparations.

Fibrin, 0.1 g., was incubated in a water bath at 35° C. with 10 ml. of a 1% solution of each enzyme and the mixture in M/15, pH 7.6, Sorensen buffer. This is the solution recommended for clinical use. Lysis of the fibrin was observed. The disappearance of the fibrin strand took place for all solutions within 75 minutes. Lysis appeared to be somewhat faster with trypsin than with either chymotrypsin or the mixture of both.

The extent of hydrolysis by the enzymes of substrates such as hæmoglobin or casein can be followed by measuring the increase in absorption at 280 μ, due to the liberation of tryptophan and tyrosine. If this is done, it will be found that on a casein substrate, chymotrypsin is twice as active, weight for weight, as trypsin, whereas on a hæmoglobin substrate the reverse is the case. However, if the degree of casein hydrolysis is determined by measurement of the amounts of split products not precipitated by trichloracetic acid, then trypsin appears more active than chymotrypsin. In either case, the lysis-potentiating effect of mixtures of the enzymes can be demonstrated. Reiser obtained successful results by applying mixtures of trypsin and chymotrypsin to fibrinopurulent necrotic lesions.

Northrop, Kunitz and Herriot[2] determined the specific activity per mg. of protein nitrogen for the two enzymes on eight different substrates; in only one case was that of chymotrypsin greater than that of trypsin. They found, however, that the total digestion of casein was greater for chymotrypsin than for trypsin. Miller[3] found that trypsin hydrolyzed 33-35 linkages in lactalbumin, whereas chymotrypsin splits 47 to 50.

In view of the fact that the relative activities of the enzymes depend on the nature of the substrate and the method of assay, it occurred to us that chymotrypsin might prove as effective a debriding agent as trypsin. The utilization of all the proteolytic enzymes of the pancreas, either singly or in mixture, would result in a much more economical enzymatic material for debridement than at present. Preliminary experiments gave very encouraging results, and a series of clinical tests were carried out.

Alpha-chymotrypsin was prepared by the method of Kunitz and Northrop as a lyophilized crystalline powder containing approximately 20% of ammonium sulfate. It was made up in a sterile way in vials. Each vial contained 250,000 units of activity. The unit is in terms of a house standard of pure, salt-free, recrystallized, lyophilized chymotrypsin, one milligram of which is defined as possessing 1000 units of activity. Each vial was accompanied by a vial containing 25 ml. of sterile, M/15 Sorensen buffer, pH 7.6, for dissolving the enzyme for application. The enzyme might also be dissolved in one ounce of 4½% carboxymethyl cellulose gel for application. Applying the enzyme as a dry powder by means of an insufflator was found to be unsatisfactory, as capillary bleeding and pain resulted from the high local concentrations of enzymes.

The enzyme was tested for toxicity. A standard preparation was dissolved in physiological saline just before use and injected (0.2 ml.) intramuscularly into rats up to levels of 200 mg./kg. and concentrations of about 40%. Severe lesions were produced at the injection site with the high dose levels, but no significant toxicity was exhibited.

The acute intraabdominal LD_{50} of the standard chymotrypsin was determined in mice. It was 45.8 ± 5.6 mg./kg.[4] Webb *et al.*[5] found the LD_{50} of crystalline chymotrypsin to be 65.1 ± 2.3 mg./kg. following intraperitoneal injection. They found no evidence of toxicity where rats had been injected subcutaneously at different dosage levels over a period of four weeks.

CLINICAL INVESTIGATIONS

Sixty patients with necrotic and suppurative lesions were treated with chymotrypsin. The clinical conditions included decubital ulcers, stasis ulcers, severe burns, chronic abscesses, osteomyelitis, carbuncles and infected wounds; the common factor in all these disorders was the presence of necrotic tissue accessible to the local action of the enzyme.

Forty cases were observed at the Ontario Hospital in Toronto, and 15 were studied at the Royal Victoria Hospital in Montreal. An additional five were private patients.

METHODS OF APPLICATION

Decubital and stasis ulcers and all superficial lesions were treated by the application of chymotrypsin, either in the form of wet dressings, in methylcellulose gel, or as an ointment dressing.

For the wet dressings, the contents of one vial (250,000 units) of chymotrypsin was dissolved in sterile buffer, making a dilution of approximately 1%, as described above. A gauze pad was soaked in this solution, then applied to the lesion and covered with an oil cloth or other impermeable material, and bandaged. These compresses were left on for a period of 30 minutes and this procedure was repeated three to four times daily. In a small number of cases, 5% chymotrypsin in petrolatum was utilized (Ontario Hospital). In the Royal Victoria Hospital cases, the compresses were applied for one hour, six times daily, for two days and then

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the chymotrypsin in methylcellulose gel (one vial of chymotrypsin in 30 g. of the gel) was applied daily and allowed to remain on the lesion for about eight hours. This method gave comparable results and required less nursing care.

RESULTS

Complete debridement occurred within 48 to 72 hours in the more superficial necrotic ulcers. The deeper decubitus ulcers required four or five days.

SIDE EFFECTS

A burning sensation or mild pain occurred in about one-third of the patients treated, but was not severe enough to warrant discontinuation of therapy. Shortening the time of application and periods between treatments resulted in disappearance of these complaints in all instances. An inflammatory reaction at the edge of the lesions occurred in two of the cases treated with the 5% suspension in petrolatum.

COMPARATIVE STUDY

Fifteen patients with a variety of chronic skin lesions were studied at the Royal Victoria Hospital in Montreal. All patients selected were over 60 years of age. The group included nine cases of decubital ulcers, five necrotic leg ulcers and one diabetic patient with multiple large carbuncles. The debriding action of chymotrypsin was compared with that of an enzyme of bacterial origin (14 cases) and of trypsin (1 case). The results of this study showed chymotrypsin to be superior in its effect in 12 instances, equal in two and inferior in one case as compared to the other preparations used. These comparative results are based only on the particular concentrations of the three enzymes used and do not permit any further conclusions as to the relative activity of these substances.

ILLUSTRATIVE CASE REPORTS

CASE 1.—F.M., a 64-year-old woman with diabetes mellitus, had had two symmetrical deep necrotic ulcers over the medial aspects of the lower legs for two years. Both ulcers were approximately 4 by 6 cm. in size.

Therapy	*Right leg, chymotrypsin*	*Left leg, bacterial proteolytic enzyme*
1st day	Much discharge	Much discharge
2nd day	Increased drainage	Increased drainage
3rd day	Necrotic centre sloughing	Necrosis still adherent
4th day	Necrosis removed, clean base and granulation; treatment discontinued	Necrosis begins to slough off
5th day	No change	Necrosis removed, clean base
8th day	Epithelization well progressed	Epithelization starting

A burning sensation was present in the right leg for the first three days of treatment.

CASE 2.—E.C., a man aged 70, diabetic, developed a large periurethral abscess. His temperature was 103° F. by mouth and the white cell count was 15,000 with 82% polymorphonuclear leukocytes. *Staphylococcus pyogenes*, cultured from the abscess, was resistant to all the common antibiotics. The patient was unable to retain food and was approaching diabetic acidosis. Incision of the abscess was followed by rapid improvement of his general health and metabolic disorder. Three weeks later, there was still a copious discharge from the abscess cavity and no evidence of healing. In addition, considerable difficulty was encountered in controlling the diabetes. Cotton batting soaked in chymotrypsin solution was then packed into the abscess cavity for 30 minutes, four times daily. Within four days the wall of the abscess was clean, and healing had started at the base of the cavity. Complete obliteration of the abscess was noted after three weeks. After this, it was found that the patient's diabetes was readily controlled on his previous regimen of insulin and diet.

CASE 3.—W.S., a man aged 56, suffered from chronic osteomyelitis of the left tibia with sequestrum formation. A sinus tract had developed about two years prior to his coming under observation, and periodically discharged seropurulent material. Eventually he developed multiple discharging sinuses, and fragments of dead bone were recovered from the sinus tract from time to time. His general physical condition was extremely poor at the time of admission to the Ontario Hospital and it was felt that he was a poor operative risk. *Staphylococcus pyogenes* in pure culture was recovered from the sinus tract initially, but contamination with *Proteus vulgaris* and *Pseudomonas aeruginosa* occurred subsequently, and there was further deterioration in the man's clinical state. His temperature remained elevated at 102° F. by mouth and there was copious purulent discharge from the sinus tract. The bacteria proved resistant to all antibiotics. At this time irrigations with buffered chymotrypsin solution were started and repeated every four hours. There was a marked decrease in the volume of purulent discharge within four days and only a thin odourless oozing was noted after six days. The temperature fell to normal and the patient's general condition improved appreciably without any additional antibiotic therapy. After three weeks of chymotrypsin therapy he was ready for surgical intervention.

DISCUSSION

The rapidity with which necrotic tissue was removed by chymotrypsin therapy was the most impressive feature of our observations. It is obvious that this rapid removal of necrotic material should shorten the course of the disease process considerably.

Another point of interest is the fact that the use of antibiotics tends to be unsatisfactory in

the presence of massive necrosis; debridement makes the base of the ulcer accessible to the action of an appropriate antibiotic. Moreover, it was noted that further use of antibiotics was often unnecessary since clean granulations appeared spontaneously in most instances, followed by normal epithelization. In some old and debilitated patients ancillary methods to promote epithelization are desirable, and scarlet red ointment was found to be suitable for this purpose. In about 50% of patients admitted to the mental hospital infra-red therapy was employed in addition to the scarlet red, and the hyperæmia plus the drying effect was found to be of value.

The eventual outcome of healing depends of course on a number of factors, including the state of the circulation and the general health of the patient. Forty-eight out of the total of 60 patients treated recovered satisfactorily. Failures were encountered in the undernourished and emaciated patients, who presented problems of management because of their mental illness. Serum proteins were determined in a number of these patients, and low albumin values, in absence of liver disease, reflected their poor nutritional state.

SUMMARY

The properties of chymotrypsin are described.

Sixty patients with acute and chronic suppurative and necrotic lesions were treated by local application of chymotrypsin, either in the form of repeated compresses of aqueous solutions, or applications of the enzyme dissolved in a methylcellulose gel. Abscesses and sinus tracts were irrigated with the buffered solution.

Superficial necrotic lesions were debrided within 48 to 72 hours, at which time clean granulations were present and epithelization had commenced. Even in deep decubital ulcers, the necrotic cores were digested and clean bases noted within five days after commencement of therapy.

The effect of chymotrypsin was compared with that of a commercially available proteolytic enzyme of bacterial origin in 14 patients with symmetrical lesions and with that of trypsin in one case. With the concentrations and methods used in this small series, chymotrypsin appeared to accomplish complete debridement more rapidly.

Illustrative case reports are presented.

The authors are indebted to Canada Packers Limited, Toronto, for laboratory investigations and supplies of the pure crystalline enzyme, and to Wyeth Laboratories, Philadelphia, for permission to publish the results of the toxicity tests on mice.

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RÉSUMÉ

La chymotrypsine est une enzyme entraite du pancréas, qui fut obtenue sous forme cristallisée pour la première fois en 1935. Elle est un sous-produit de la purification de la trypsine et ses propriétés fibrinolytiques se rapprochent beaucoup de celles de cette autre enzyme. Les auteurs l'ont employée comme agent de débridement chez 60 malades présentant des lésions suppurées ou sphacélées, aiguës ou chroniques, au moyen de compresses humides ou de suspension dans un gel de cellulose. La nécrose superficielle disparut entre 48 et 72 heures, laissant voir un tissu de granulation propre sur lequel l'épithélium commençait à s'étendre. Même dans les plaies de lit profondes, les bourbillons nécrosés furent liquéfiés en 5 jours, laissant une base bien nette. Dans une comparaison effectuée sur une basse échelle de l'activité de la chymotrypsine et des enzymes protéolytiques d'origine bactérienne, elle sembla accomplir la tâche plus rapidement que les autres produits. Des observations sont citées à l'appui.

MEPROBAMATE AS ADJUVANT THERAPY IN HYPERTENSION

Dunsmore *et al.* (*Am. J. M. Sc.*, 233: 280, 1957) found that meprobamate provided symptomatic relief of varying degrees in 19 of 21 hypertensive patients. Nine of these patients previously or subsequently treated with Rauwolfia serpentina failed to obtain similar symptomatic improvement and experienced undesirable side effects.

Side effects were minimal. Anorexia developed in four patients, a symptom not previously associated with meprobamate therapy. Allergic or toxic effects were not evident in this group. Fall in resting diastolic blood pressure was recorded in 9 patients, but none to a normal level; further evaluation of this phenomenon is suggested.

Hypertensive patients treated with meprobamate experienced more marked and consistent symptomatic improvement than did a similar group of patients treated with Rauwolfia preparations.

Side effects attributed to ganglionic blocking agents seemed to be decreased by the addition of meprobamate, but further observations on this phenomenon are necessary.

Meprobamate is not recommended as a substitute for antihypertensive therapy, but, as this preliminary study indicates, it may be a useful adjuvant in providing symptomatic relief to the hypertensive patient.

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THE INFLUENCE OF ASCORBIC ACID UPON THE LIVER

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SOON AFTER THE ISOLATION and synthesis of vitamin C, the effect of scorbutogenic diets upon the liver was studied by several workers. Bessey, Menten and King[1] observed fatty degeneration of the liver in many of the guinea pigs they studied and later Russell and Callaway[2] confirmed this. The diet employed by this latter group of workers contained 3.6% fat. Lichtman[3] criticizes the general experimental studies into the relationship of ascorbic acid to the liver because one such study employed a diet containing 20% fat.[4] However, the one study in question is disqualified as a study of scurvy, not because of the high fat content of the diet, but because animals receiving ascorbic acid developed lesions in the liver and so did rabbits (an animal in whom scurvy cannot be induced).

In more recent years, the subject of ascorbic acid and the liver has receded into obscurity, so that only passing mention is made of it in one monograph on the liver[3] and it is not indexed in three others.[5-7] This may be partly because the bulk of animal research in nutritional liver disease has been done in animals able to synthesize their own ascorbic acid and hence not suitable for studying the effects of its depletion. Attention has been directed to diets deficient in protein. Himsworth and Glynn[8] in 1944, integrating the findings of previous workers,[9, 10] pointed out that two fundamental pathological processes exist. One is a fatty degeneration related to choline deficiency; the other is massive necrosis initiated by an abnormal intake of cystine. Superimposed upon these basic mechanisms are several factors which, although not fundamentally etiological, have the property of ameliorating or enhancing the lesions produced by them. These have been reviewed recently by Sherlock[5] and include vitamin E, the degree of saturation of the fatty acids in the diet, antibiotics, thyroid and antithyroid drugs.

As the etiology of many cases of human cirrhosis of the liver is still not apparent, it becomes important to look beyond cystine and choline for other etiological factors. As man is susceptible to ascorbic acid depletion and the early studies of the influence of such depletion upon the liver suggest its importance, it becomes imperative to clarify the status of this vitamin in nutritional liver disease.

MATERIALS AND METHODS

A total of 115 adult guinea pigs obtained from three separate sources was employed in the study. Nearly all these animals were in the weight range of from 250 to 500 g. and the sexes were equally represented. A basic scorbutogenic[11] diet* was fed to all animals and supplemented by various agents according to the experiment under consideration. The quantity of the diet offered each day was determined by the appetites of the animals on the previous day, and the control group was pair-fed with a scorbutic group. At the outset the animals consumed about 25 g. of feed each day and this was well sustained until the last few days of life, when it fell off rapidly. The guinea pigs were segregated in open-top cages into the following sub-groups:

1. Twelve animals fed the scorbutogenic diet for 42 days with ascorbic acid powder liberally added.
2. Twenty-three animals fed the scorbutogenic diet for periods varying from 21 to 30 days.
3. Twenty-five animals fed the scorbutogenic diet for periods varying from 21 to 30 days. They were then given a single intraperitoneal injection of 75 mg. of sodium ascorbate followed by the liberal addition of powdered ascorbic acid to the diet until they were sacrificed 1 to 5 days later.
4. Twenty-five animals identical to group 3, except that they were sacrificed at intervals varying from 7 to 27 days after beginning ascorbic acid therapy.
5. Ten animals fed the scorbutogenic diet for 28 days with choline chloride added to provide 0.3 g. per animal per day.
6. Ten animals fed the scorbutogenic diet for periods of from 27 to 28 days with cystine added to provide 0.3 g. per animal daily.
7. Ten animals fed the scorbutogenic diet for periods of 26 to 28 days with cystine and choline chloride added to provide 0.3 g. of each per animal per day.

No difficulty was encountered in adding the ascorbic acid powder or the choline chloride to the basic diet. The physical properties of cystine resulted in a tendency for it to gravitate to the bottom of the food trays, and this was partly overcome by frequently mixing up the food each day when cystine was employed.

At the end of the various experimental periods the animals were sacrificed by stunning. Their livers were removed and examined in the gross and material selected for histologic preparations. One block was fixed in 10% formalin for fat studies and another in Bouin's solution for paraffin sections. A section from each animal was stained with Mallory's phosphotungstic acid hæmatoxylin, Laidlaw's reticulin stain and Scharlach R for fat. The sections for reticulin studies were cut at 4 μ. Certain other stains were employed when it was felt they were indicated.

In the microscopic studies of the sections certain methods of grading the morphologic findings were adopted. Acute non-fatty parenchymal degenerations, necrosis and reticulin production associated with post-necrotic scarring were simply recorded as present or absent. The diffuse changes of fatty degeneration and reticulin dissolution were graded + to ++++, + representing the earliest appearance of abnormality and

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*"Miracle Rabbit Pelletts", sold by Ogilvie Flour Mills, Montreal. Analysis: protein 16.5%, fat 4.0%, fibre 9.0%, cystine 0.3%, choline 0.02%.

TABLE I.—ILLUSTRATING THE NUMBER OF ANIMALS IN EACH EXPERIMENTAL GROUP SHOWING THE VARIOUS MORPHOLOGICAL FEATURES

Group experimental procedure	Number of animals	Fatty degeneration					Acute non-fatty hepato-cellular degeneration	Massive necrosis	Reticulin change				
									Dissolution				Production after necrosis
		0	+	++	+++	++++			0	++	+++	++++	
1. Scorbutogenic diet 42 days with added ascorbic acid powder	12	12	0	0	0	0	0	0	12	0	0	0	0
2. Scorbutogenic diet for periods varying from 21 to 30 days	23	3	8	6	3	3	19	7	4	12	4	3	0
3. Scorbutogenic diet as in Group 2. Then ascorbic acid over periods of 1 to 5 days	25	9	8	2	4	2	9	7	7	8	5	5	7
4. Scorbutogenic diet as in Group 2. Then ascorbic acid over periods of 7 to 27 days	25	18	7	0	0	0	3	8	7	8	9	1	8
5. Scorbutogenic diet for 28 days with added choline chloride	10	0	2	5	3	0	9	8	0	0	0	10	0
6. Scorbutogenic diet for 27 to 28 days with added cystine	10	0	2	2	5	1	7	7	0	0	2	8	0
7. Scorbutogenic diet for 26 to 28 days with added cystine and choline chloride	10	1	5	2	1	1	8	6	0	1	3	6	0

++++ the most extreme. The minor abnormalities of + reticulin dissolutions were felt to be too difficult to assess objectively and + changes in the reticulin were therefore considered within normal limits in the final analysis.

The term "fatty degeneration" is used to describe the deposit of stainable lipids within liver parenchymal cells.

RESULTS

The 12 control animals (Group 1) thrived on their experimental regimen, and thorough study of their livers revealed no abnormalities. The salient pathological changes encountered in the animals subjected to scurvy were in the parenchymal cells and the hepatic reticulin. These are summarized in Table I and consisted of the following:

1. *Acute non-fatty hepato-cellular degenerations.*—In scorbutic animals cloudy swelling and hyaline, droplet and vacuolar degenerations were a fairly consistent finding. Such changes were patchy in distribution, often punctate (Fig. 1) but sometimes massive and progressing to massive necrosis. After therapy with ascorbic acid these changes were shown to be reversible in a few days. The occasional finding of hyaline degeneration persisting longer was exclusively in relation to areas of massive necrosis.

2. *Massive necrosis.*—As Table I shows, massive necrosis was common in scorbutic livers. It was patchy, never zonal, and varied in extent from two or three lobules to half a liver lobe. Sometimes it was hæmorrhagic. The portions of the liver most susceptible to necrosis were the subcapsular regions, especially at the apex of a lobe. After ascorbic acid therapy these lesions assumed the characteristic pattern of post-necrotic scarring, but without such therapy they failed

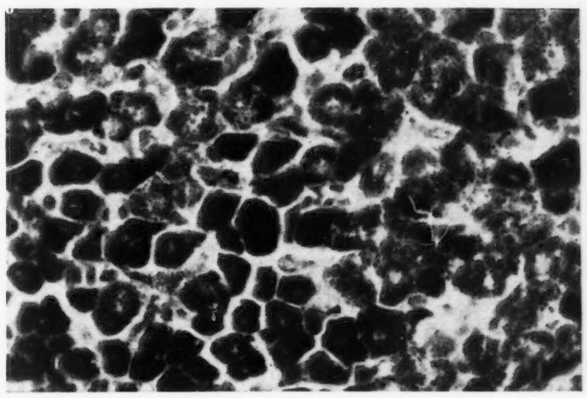

Fig. 1.—High power view of a scorbutic liver. Note the hyaline degeneration of parenchymal cells (Mallory's phosphotungstic acid hæmatoxylin).

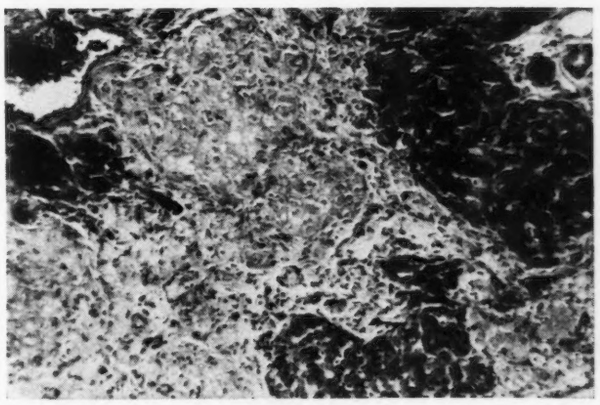

Fig. 2.—Low power view of a scorbutic liver three days after the onset of treatment with ascorbic acid. Note the islands of intact liver parenchyma and the massive necrosis taking on the form of post-necrotic scarring with abundant production of collagen (Mallory's phosphotungstic acid hæmatoxylin).

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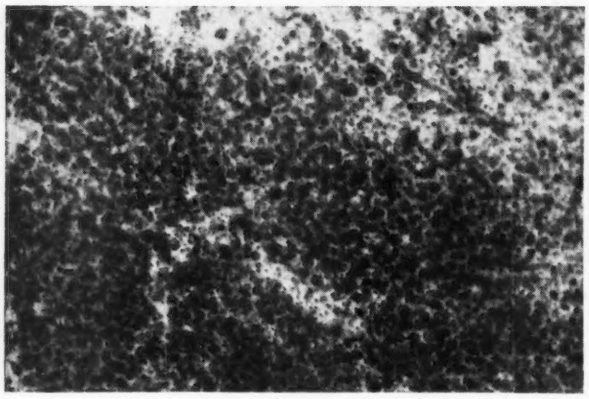

Fig. 3.—Low power view of a section of liver in scurvy. Note the extensive fatty degeneration (Scharlach R).

to organize. Fig. 2 illustrates a typical instance of post-necrotic scarring.

3. *Fatty degeneration.*—It was exceptional for fatty degeneration to be absent. Sometimes the deposit of fat was so extensive as to solidly fill the entire liver (Fig. 3). In its lesser degrees the fat tended to be peri-central or peri-portal. With the onset of ascorbic acid therapy, resorption of the lipid was rapid. Intermediary stages of resorption were characterized by a decreased intensity of staining and margination of the fat along the periphery of a fat vacuole. In some instances the lipid had extravasated extracellularly to form fatty cysts. These had the features described by Hartroft and Sellers[12] in choline-deficient rats and were resorbed when ascorbic acid therapy was instituted. The residual lipid listed in Group 4 of the table was of the extracellular type.

4. *Changes in hepatic reticulin.*—With the onset of scurvy the reticulin in the liver lobules of most of the animals underwent a greater or lesser degree of dissolution, although the reticulin of the liver capsule and the larger portal tracts remained relatively intact. Nevertheless, the parenchymal cells did not become disrupted in their alignment. Fig. 4 illustrates the normal pattern of hepatic reticulin radiating out between the parenchymal cells from the central veins. Fig. 5 is an example of +++ reticulin dissolution in scurvy. This dissolution was often independent of either fatty or non-fatty hepato-cellular degeneration or of necrosis. It sometimes occurred in animals whose livers were otherwise normal on histological examination. When ascorbic acid therapy was begun, there was little or no influence upon the state of reticulin dissolution even after long periods of time (see Table I). This was in sharp contrast to the reversibility of the degenerative changes described in the parenchymal cells.

Apart from participating in the generalized form of reticulin dissolution, the reticulin in

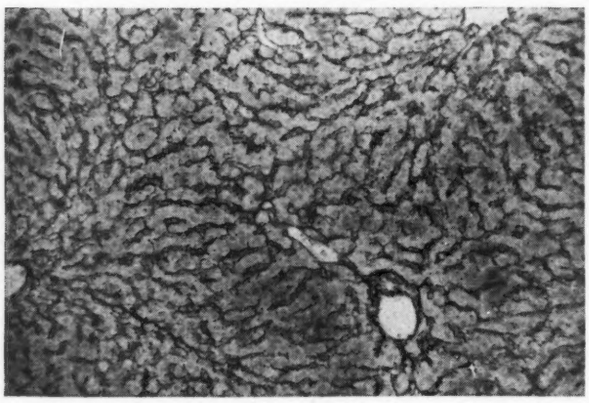

Fig. 4.—Low power photomicrograph of the hepatic reticulin in a normal guinea pig. Compare with Fig. 5, which shows the influence of ascorbic acid depletion upon the reticulin (Laidlaw's reticulin stain).

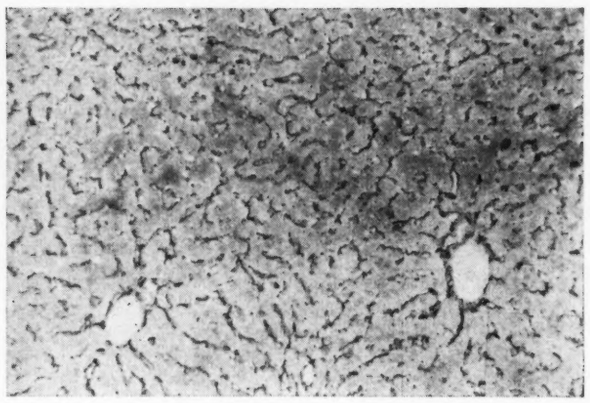

Fig. 5.—Low power view of the reticulin change seen in the liver in scurvy. Note the dissolution, in this instance, of grade +++ degree. Compare with the normal reticulin in Fig. 4 (Laidlaw's reticulin stain).

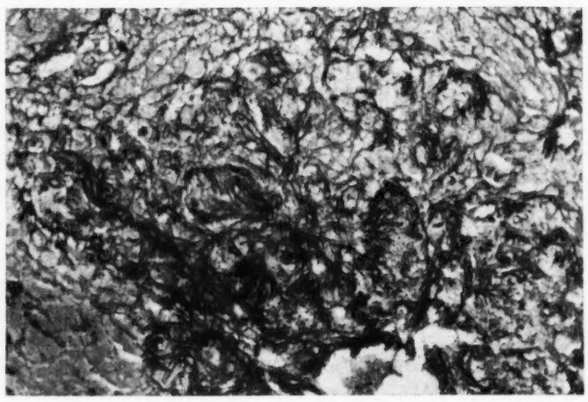

Fig. 6.—A high power view of the proliferation of reticulin in an area of massive necrosis in the liver in scurvy. Reticulin appears only after the institution of ascorbic acid therapy. This is from the same patch of post-necrotic scarring illustrated in Fig. 2 (Laidlaw's reticulin stain).

areas of necrosis revealed no particular feature. It did not collapse. After even a brief period of ascorbic acid therapy, however, there was a prolific increase in both reticulin (Fig. 6) and collagen (Fig. 2) in these areas, with resultant post-necrotic scarring.

EFFECT OF CHOLINE AND CYSTINE UPON THE LIVER IN SCURVY

As Table I indicates, the addition of cystine or choline or a combination of these agents to the diet of animals developing scurvy in no way inhibited the lesions in the liver produced by scurvy. Indeed, the lesions in these 30 animals (Groups 5, 6 and 7) were often more pronounced than in the scorbutic groups.

DISCUSSION

Fatty Degeneration of the Liver

In this study the finding of fatty degeneration of the liver in scorbutic guinea pigs by Bessey and his associates[1] has been amply confirmed. It occurs in as little as three weeks from the onset of a diet low in fat but deficient in ascorbic acid.

Fatty degeneration of the liver in scurvy is not inhibited by choline; it is rapidly reversed by ascorbic acid replacement. On these grounds it may be concluded that choline and ascorbic acid have separate effects upon fat metabolism in the liver cell.

This is not the first time it has been shown that ascorbic acid has lipotropic properties. Human atherosclerotic plaques and xanthomata have decreased in size or disappeared under its influence,[13] and recent studies show that it can effect resorption of scurvy-induced atherosclerotic plaques in the guinea pig.[14]

One can but speculate at present as to the mechanism of the fatty degeneration observed in scurvy. The finding of an increased rate of incorporation of radioactive acetate into cholesterol in the liver, adrenals and arteries in scorbutic guinea pigs *in vivo*[15] is of great interest, however.

Acute Non-Fatty Degenerations and Massive Necrosis

These findings in the liver in scurvy have not been previously reported. They resemble the changes found in the liver of cystine-deficient animals.[3] The fact that the degenerative phenomena were reversible with ascorbic acid therapy and were not prevented by cystine indicates that they were a manifestation of ascorbic acid depletion independent of cystine.

Reticulin Changes

Of prime importance in nutritional liver disease is the reversibility of the lesions. In zonal necrosis, Himsworth[8] believes that a rim of preserved parenchymal cells may hold open the reticulin framework of the lobule as an accurate scaffolding upon which the lobule can be rebuilt. He points out that in massive necrosis no such rim of parenchyma survives and in those lobules where all the cells are dead there is nothing either to prevent collapse of the reticulin or from which new parenchyma can be regenerated.

Hartroft[16] believes that the diffuse hepatic fibrosis following prolonged fatty degeneration of the liver is the result of a condensation of stroma at the sites of rupture of fatty cysts. He holds that these fatty cysts are formed by the extracellular extravasation of fat from overloaded parenchymal cells.

Thus, in the cirrhosis of post-necrotic scarring and that following prolonged fatty degeneration, the reticulin stroma has been held to be of fundamental importance. In spite of this, very little investigation into the subject of the hepatic reticulin has been made, and it is felt that the reticulin and collagen changes observed in scurvy contribute to this matter as well as shedding light on the characteristics and behaviour of reticulin in general.

In 1926, Wolbach and Howe[17] demonstrated that scurvy affects the intercellular materials. The present study demonstrates that ascorbic acid is necessary for the preservation and formation of the hepatic reticulin and in ascorbic acid depletion extreme degrees of reticulin dissolution occur. However, the general architecture of the liver lobule does not appear to suffer as a result. Contrary to the concept of Himsworth[8] and of Hartroft,[16] who postulate a condensation and collapse of reticulin secondary to parenchymal destruction, this study shows that only fragmentation and dissolution of reticulin occur in areas of necrosis. Only when ascorbic acid therapy is given is there a dense laying down of reticulin and collagen. Thus there is not a condensation of old reticulin in necrotic areas but rather a deposition of new,

and this new reticulin is dependent upon ascorbic acid.

It is apparently not possible to regenerate the reticulin of scurvy when ascorbic acid is replaced unless parenchymal destruction has occurred. This confirms the finding of Wolbach[18] that reticulin and collagen are formed by fibroblastic activity.

The Liver in Human Scurvy

Reviewing the older literature on human scurvy, it is seen that severe liver disease is a feature. Thus Aschoff and Koch[19] regarded advanced fatty degeneration of the liver as characteristic. These may possibly have been cases of a more general type of malnutrition. Stephen and Tidswell,[20] however, reported a case of extreme fatty degeneration of the liver in a seven-month-old scorbutic child who had had a good milk intake from birth.

SUMMARY

Scurvy manifests itself in the liver by fatty degeneration, acute non-fatty hepato-cellular degenerations, massive necrosis and changes in the hepatic reticulin. None of these lesions are prevented by cystine or choline or a combination of them. Some of them are reversible with ascorbic acid replacement.

Ascorbic acid must now be considered as a factor ranking in importance with cystine and choline in nutritional liver disease. It is not in the category of those factors which simply enhance or ameliorate the hepatic changes of cystine or choline deficiency.

Distinct from cystine and choline, ascorbic acid has a primary influence upon hepatic reticulin and collagen formation.

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RÉSUMÉ

L'atteinte hépatique dans le scorbut se manifeste par une dégénérescence graisseuse, une dégénérescence hépatocellulaire aiguë mais non graisseuse, une nécrose généralisée et des altérations dans la réticuline hépatique. La cystine ou la choline, seules ou combinée, ne peuvent influencer ce processus en aucune manière. Certaines de ces lésions cependant sont supprimées par l'administration d'acide ascorbique. La vitamine C devrait donc être considérée au même rang que la cystine et la choline dans les atteintes hépatiques de carence nutritive. Elle n'appartient pas à la catégorie de ces substances qui enraient ou améliorent les lésions hépatiques résultant de la déficience de cystine ou de choline. Contrairement à ces dernières, l'acide ascorbique exerce une influence fondamentale sur la formation de la réticuline et du collagène hépatiques.

THE GENESIS OF THE "PRESYSTOLIC" MURMUR IN MITRAL STENOSIS

The total experience gained by examining the functioning mitral valve suggests that stenosis alters the basic mechanism of intra-atrial leaflet displacement at the time of valve closure.

When the free edges of the leaflets are fixed at the commissures but the elasticity of the central portion is not compromised, a gross vibration is palpable during intra-atrial displacement. It has been a consistent experience that this gross vibration occurs only in those patients in whom a presystolic murmur is heard.

When the leaflets are inelastic intra-atrial ballooning and associated vibrations are not observed. These patients do not have a presystolic murmur.

Phonocardiographic registrations during right or left heart catheterization show that the "presystolic" murmur originates during the first rise in ventricular pressure after the onset of the isometric period. The murmur therefore is considered systolic in time.

This concept of the genesis of the presystolic murmur is consistent with the acoustic qualities and the theoretical factors related to the intensity, pitch, and duration of sound in a stretched two-dimensional membrane.—H. T. Nichols *et al.*: *Am. Heart J.*, 52: 379, 1956.

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Case Reports

DYSPHAGIA DUE TO A LOWER ŒSOPHAGEAL RING

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IN RECENT YEARS several cases of dysphagia have been reported which seem to represent a characteristic and previously unrecognized clinical entity.[1-3] The patients complain of a sudden, intermittent dysphagia. X-ray studies reveal a smooth concentric narrowing in the œsophagus situated a few centimetres above the diaphragm. No inflammation, ulceration, scarring or neoplasia is seen at endoscopy.

A report of such a case is presented here, together with a brief discussion of this interesting syndrome.

Clinical findings.—A 52-year-old white business executive was admitted to the Montreal General Hospital in January 1956. For four to five years he had complained of sudden, intermittent difficulty in swallowing. He described a painful sticking sensation directly behind the fourth costo-chondral junction. The attacks occurred while eating solid food. The distress was moderately severe on most occasions. The sticking pain lasted for a few minutes until he felt the bolus pass through. An aching sensation persisted for as long as an hour or more. On one occasion, the substernal pain was agonizing. He thought he was going to choke and believed he was suffering from a heart attack. He vomited violently and felt the obstruction dislodge, with immediate relief. During early attacks he drank water in an effort to force through the bolus. This was successful on occasion but at other times aggravated the sticking pain. During later episodes he was afraid to swallow anything until he felt that the obstruction was relieved. The symptoms tended to appear when he was working under extra strain and he believed that tension was somehow responsible. Close questioning showed that at such times he tended to bolt his food without cutting or chewing it carefully. Beefsteak and dry white poultry meat were particularly offensive. He had lost 10 lb. in weight during the previous year. The history was not otherwise helpful.

On physical examination he seemed to be a healthy man of stated age. There was no fever. The blood pressure (150/90 mm. Hg) was slightly elevated, but the heart was not enlarged and the rhythm was regular. Physical examination was not otherwise remarkable.

The laboratory findings (red cell count about 5 million; Hb value 15.2 g. %; white cell count 4500; differential count: urinalysis—sp. gr. 1.016, no albumin, sugar, red cells, white cells or casts; stool for occult blood negative; fasting blood sugar 113 mg. %; urea nitrogen 11 mg. %; bilirubin 0.3 mg. %; cephalin flocculation negative; electrocardiogram, normal curves; barium series, gall-bladder visualization and chest radiograph were all normal.

Radiological findings.—The lower œsophageal ring was demonstrated by fluoroscopic examination after a swallow of barium. The patient fasted after his evening meal. The following morning barium paste was administered with the patient in the prone left oblique position. When the barium reached the lower end of the œsophagus, he was asked to take a deep breath and bear down (the Valsalva manœuvre). The lower end of the œsophagus was seen to dilate. This dilatation was considered to be the normal ampulla of the œsophagus. A symmetrical ring-like narrowing was seen at the level of the ampulla when the œsophagus was well distended with barium. Spot films taken at this time are shown in Fig. 1. The patient was next asked to swallow a large gelatin capsule filled with barium (Fig. 2). The passage of the capsule was delayed at the site of the ring. The patient was conscious of the sticking substernal pain he had de-

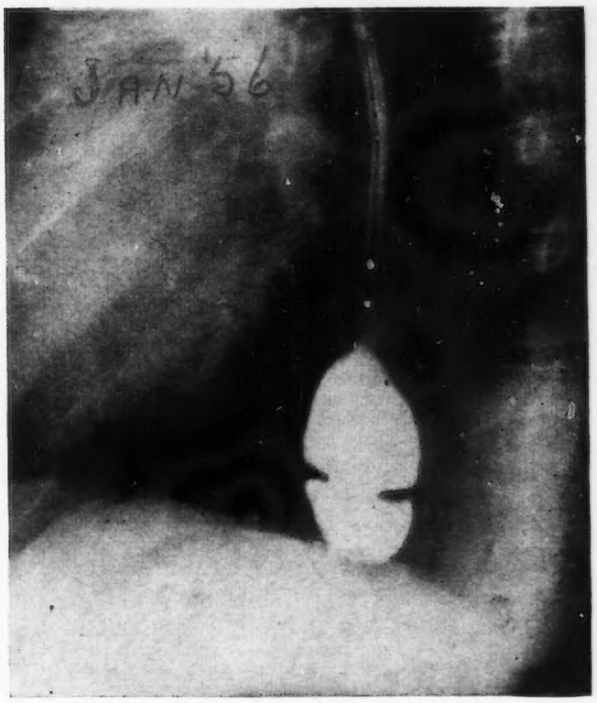

Fig. 1

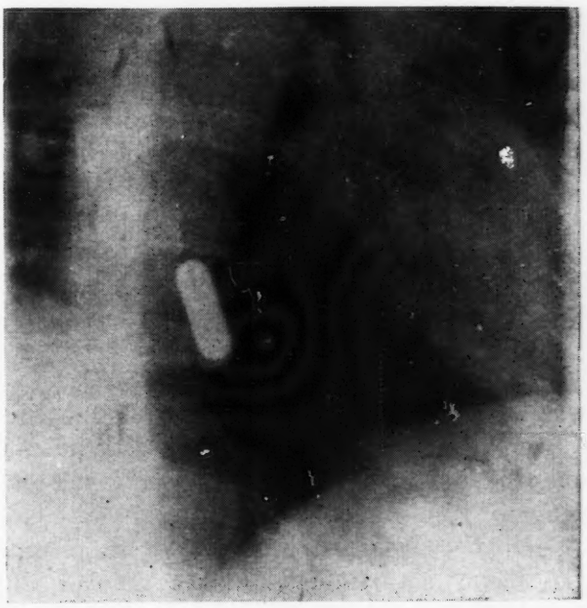

Fig. 2

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scribed previously. The capsule then passed through the ring and the substernal discomfort disappeared. With the patient in the upright position a small swallow of barium passed easily down the œsophagus and into the stomach. It was clearly necessary to position the patient and to distend the œsophagus in order to demonstrate the ring.

Endoscopic findings.—An œsophagoscopy was performed by Dr. E. E. Scharfe, using a No. 10 œsophagoscope. The œsophageal mucous membrane appeared entirely normal. There was no evidence of inflammation, ulceration, scarring or neoplasia. The œsophagoscope passed easily into the stomach at 41 cm. No evidence of constriction was demonstrated on this examination.

Treatment.—The nature of the condition was explained to the patient. He was advised to cut and chew his food carefully and to eat slowly. His symptoms were almost completely relieved. During the past six months he has had only a few minor episodes of dysphagia. Fluoroscopic examination of the œsophagus was repeated in September 1956. The œsophageal ring remained unchanged.

DISCUSSION

The lower œsophageal ring occurs in both sexes and usually in patients over 50 years of age. It is probably a common disorder but often overlooked. Schatzki and Gary[3] made spot films of the distended lower œsophagus in 368 consecutive patients sent for gastro-intestinal examination; 17 showed the characteristic ring and two complained of dysphagia. The diameter of the ring varies from patient to patient but has remained remarkably constant in individual patients over several years. The diameter of the ring seems to determine whether or not dysphagia will occur. Thus, narrow rings invariably produce dysphagia, while wide rings never do so. Medium-bore rings may or may not produce dysphagia, depending on the eating habits of the patient.

The nature of the lower œsophageal ring is obscure. Ingelfinger and Kramer[1] suggested that an overactive lower œsophageal sphincter is responsible. One of their cases came to surgery. Thickening of the muscle layers was demonstrated at the site of the ring. It was covered by normal œsophageal mucosa. On the other hand, Schatzki and Gary[3] believe that the ring is a passive structure, representing a short annular segment of the lower œsophagus which fails to distend as readily as the portions above and below. One of their cases also came to surgery. No thickening or change in consistency was felt at the site of the ring. A biopsy from this area showed normal œsophageal tissue, but unfortunately the muscle layers were not examined.

Annular contractions in the lower œsophagus and hiatus hernia may at times simulate the radiological appearance of the lower œsophageal ring; indeed, the ring is associated with hiatus hernia in some cases. However, in patients with dysphagia the clinical and radiological findings are clear-cut and the diagnosis is not difficult.

Treatment is classic in its simplicity. The nature of the dysphagia is explained and the patient is advised to eat slowly, chew carefully and swallow a small amount at a time. In this way, further symptoms are obviated in the majority of patients. A few with extremely narrow rings may require plastic surgery. Attempts to increase the diameter of the rings by drug therapy or bouginage have not been successful.

Intermittent dysphagia associated with a lower œsophageal ring seems to represent a definite and not uncommon clinical syndrome. It is important to differentiate this disorder from other causes of dysphagia.

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CO-EXISTING BRONCHOGENIC CARCINOMA AND ACTIVE PULMONARY TUBERCULOSIS
REPORT OF FIVE CASES

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THE ASSOCIATION of carcinoma of the lung with active pulmonary tuberculosis has received a great deal of attention in the medical literature during the past five years. This combination, once considered extremely rare, has been reported by at least six observers between 1952 and 1956. In February 1952, Goldberg and his associates[1] described five cases, and suggested certain clinical features that might be helpful in the diagnosis of the two co-existing diseases. Exactly one year later, Nuessle[2] published four additional case reports and suggested that, at times, bronchogenic carcinoma may reactivate pre-existing pulmonary tuberculosis. In August 1955, Shafran and Kavee[3] reported the antemortem diagnosis of associated bronchogenic car-

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cinoma and pulmonary tuberculosis, and its confirmation in six patients, all of whom were men between the ages of 45 and 69. A few months later, Hauser and Glazer[4] collected 10 cases of concomitant pulmonary tuberculosis and bronchogenic carcinoma, and discussed at length the roentgenographic features that suggested the carcinomatous element. In June 1956, Weissman[5] reported, as part of a larger group, 11 cases in which bronchogenic carcinoma co-existed with pulmonary tuberculosis; and he emphasized that, in such cases, the physician may be misled by roentgenographic improvement resulting from antimicrobial therapy. Finally, only a few months ago, Bender[6] described in great detail 15 cases of co-existing primary pulmonary carcinoma and active pulmonary tuberculosis.

It will readily be appreciated that, with more than 50 such cases reported in less than five years, the association of these two diseases must no longer be considered excessively rare, and the physician should be very much on his guard to ensure that neither condition is missed. There seems to be a certain unanimity of opinion among various observers as to why these two diseases are now being more frequently discovered in combination. It is the general consensus that carcinoma of the lung is a disease of middle and later life; that more patients with tuberculosis are recovering from that disease and living their normal life-span; and that, statistically speaking, there is therefore more likelihood of carcinoma of the lung occurring in the older patient with pulmonary tuberculosis. As is usually the case, this is probably not the complete answer. There is little doubt that the recent increase in interest in bronchogenic carcinoma has contributed to this state of affairs by stimulating more exhaustive investigation and more accurate diagnosis; and there are even those[2, 7] who would suggest that there is an etiological association between bronchogenic carcinoma and pulmonary tuberculosis. In any case, since tuberculosis has become a relatively non-fatal disease, and since carcinoma of the lung remains one of our most potent killers, it becomes important for us as physicians to be certain, as far as is humanly possible, that we are not overlooking the presence of carcinoma of the lung in any of our patients with pulmonary tuberculosis.

It is therefore our desire to emphasize this point by adding five cases of combined pulmonary tuberculosis and malignancy to those already described in the literature. In two of these cases, the co-existence of tuberculosis and malignancy was completely unsuspected ante mortem, the true state of affairs becoming clear only at necropsy. In two cases the combination was suspected, in one on roentgenological grounds and in the other after bronchoscopy. In the fifth case, a pulmonary neoplasm *uncomplicated by tuberculosis* was suspected, and the presence of the two diseases was discovered at thoracotomy. Three of these cases originate in the Nova Scotia Sanatorium, Kentville, Nova Scotia, while the other two are from the Point Edward Hospital, Sydney, Nova Scotia.

The summaries of the five case histories are as follows:

CASE 1.—D.J. was a 52-year-old man. Four months before admission he had noted easy fatigue, loss of appetite and weight, and right-sided chest pain. He sought medical attention in February 1943, and at that time a roentgenogram revealed disease in the right lung. He was admitted to the Nova Scotia Sanatorium on February 10, 1943. X-ray examination a few days later revealed bilateral upper-lobe disease with a cavity in the right apex. A specimen of sputum was *positive* for tubercle bacilli on culture. Treatment consisted of modified bed rest without collapse therapy. Over the next few months, until August 1943, there was significant clinical and roentgenological improvement. However, on August 23, the patient was found dead in his bed at 6 a.m., "lying peacefully on his side". Necropsy revealed chronic interstitial pneumonia, silicosis, bilateral pulmonary tuberculosis, chronic bronchitis, bronchiectasis with vesicular emphysema, *and* a small bronchogenic carcinoma of the papillary adenocarcinoma type, in the lower-lobe branch of the left main bronchus.

CASE 2.—L.O. was a 58-year-old man. He had previously been a patient in the Nova Scotia Sanatorium, from November 18, 1950, to August 28, 1951. At that time, he was found to be suffering from far advanced, bilateral pulmonary tuberculosis, and several specimens of sputum were positive for tubercle bacilli on concentration and culture. Treatment had consisted of modified bed rest, streptomycin with para-aminosalicylic acid, and a five-rib left thoracoplasty. He had left hospital against advice on August 28, 1951, only to be readmitted on January 22, 1952; at that time, two specimens of sputum were *positive* for tubercle bacilli. Treatment was reinstituted, but, six months later, x-ray examination of the chest revealed a discrete, rounded shadow above the right diaphragm in the cardiophrenic angle, completely separate and removed from the tuberculous lesion. In retrospect, this had been present in a roentgenogram taken six months earlier, but had been very small; in the interval, it had enlarged greatly. Although bronchoscopy did not provide corroboration, a pulmonary neoplasm was suspected. Because of the presence of a thoracoplasty on the left side, and a probable tumour on the right, it was considered that no further surgical interference was warranted, and the patient was discharged in August 1952. On November 4, 1952, he was readmitted *in extremis*. At this time, one specimen of sputum was *positive* for tubercle bacilli on culture. The patient suffered from increasing dyspnœa and died on November 23, 1952. Necropsy revealed a peripherally situated bronchogenic carcinoma, with metastases to the mediastinum and liver.

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CASE 3.—A.M. is a 42-year-old man. In 1941 he began to suffer from cough, sputum, and loss of weight and appetite. Chest roentgenogram at that time revealed evidence of pulmonary tuberculosis, and he was admitted to hospital, where left artificial pneumothorax was induced and intrapleural pneumolysis carried out. From October 1942 to October 1944, the patient lived at home and had pneumothorax refills as an outpatient until re-expansion. In 1943, he was allowed to resume work as a bus-driver. Six years later, in October 1949, x-ray examination of the chest revealed new disease in the right lung. In February 1950, the patient was therefore again admitted to hospital, and *right* pneumothorax was instituted. However, his condition did not improve; there was continued weight loss, and cough, sputum, and fever were noted. On August 6, 1953, he was admitted to the Nova Scotia Sanatorium, where a chest roentgenogram revealed chronic bilateral pulmonary disease, with possible cavitation on the right, and an opacity on the left, which, in the lateral view, suggested a tumour mass. On August 21, 1953, bronchoscopy revealed a fungating mass in the left upper lobe bronchus, invading the lower lip of the orifice and extending into the main bronchus. Histological examination of a specimen removed at this examination revealed an epidermoid carcinoma. At this time, two specimens of sputum were *positive* for tubercle bacilli on culture. On September 8, 1953, a left radical pneumonectomy was performed. Gross and microscopical examination of the surgical specimen revealed infiltration of the left upper lobe by a moderately well-differentiated epidermoid carcinoma. This patient is at present alive and well.

CASE 4.—L.R. is a 55-year-old man. He was admitted to the Point Edward Hospital on June 7, 1954, for investigation of an abnormal shadow in the apex of the right lung. He was symptom-free, but investigation had been advised following a mass x-ray survey in May 1954. On admission, the sputum was negative for tubercle bacilli on direct smear and concentrate, and specimens collected for culture at this time were later found to be negative. Bronchoscopic examination was carried out on June 8, 1954, and no abnormalities were noted. Specimens of sputum as well as specimens of secretion collected at bronchoscopy were examined cytologically with normal findings. Planigraphic studies of the right upper lobe revealed a large, rounded, circumscribed solid density in the right apex. There was evidence of calcification in the right lung field, but not apparently within the confines of the lesion. In view of our strong suspicion that this patient had a pulmonary neoplasm, and because of the length of time that might be required to exclude tuberculosis, exploratory thoracotomy was carried out on July 8, 1954, and the upper and middle lobes of the right lung were resected. Gross and histological examination of the surgical specimen revealed the presence of subacute fibrocaseous tuberculosis *and* carcinoma of the lung, "most likely secondary from the alimentary tract". After several thorough investigations in an effort to discover the site of the primary lesion, the sections were re-examined by several pathologists, and it was then conceded that the histological appearance of this carcinoma was quite consistent with a primary origin in the lung. The patient received adequate institutional treatment for his pulmonary tuberculosis, including antimicrobial therapy, and, since his operation, he has been clinically well, without evidence of recurrence of the pulmonary neoplasm or of progression of an extrapulmonary primary growth, if one had actually existed.

CASE 5.—T.R. was a 42-year-old man. He was admitted to the Point Edward Hospital on February 2, 1953, with far advanced, bilateral pulmonary tuberculosis; the sputum was *positive* for tubercle bacilli on direct smear and concentrate. Bronchoscopic examination in April 1953, and again in July 1954, failed to reveal any evidence of endobronchial disease. Shortly after admission, treatment was begun with modified bed rest, streptomycin, PAS, isoniazid and artificial pneumoperitoneum. The latter was subsequently discontinued because of discomfort and apparent lack of benefit. The patient's condition remained generally stationary, with sporadic improvement, for well over two years, but he never showed sufficient clinical or roentgenographic evidence of recovery to warrant his discharge from hospital, even for domiciliary treatment. In September 1955, x-ray examination revealed bilateral extension of disease. Although treatment was intensified, there was noted, from this time on, a continuous, general, and rapid deterioration. On November 15, 1955, roentgenograms revealed gross extension of disease in the right lung, and the patient died quietly on November 19, 1955. Necropsy was performed shortly after death; gross and histological examination of the lungs revealed bilateral fibrocaseous tuberculosis *and*, in the left lung, a poorly differentiated tumour, described as either a reticulum cell sarcoma or an anaplastic carcinoma.

COMMENT

From the reports described above, it seems clear that in some cases the co-existence of carcinoma of the lung with active pulmonary tuberculosis can be reasonably suspected; while in others there is, under ordinary circumstances, little evidence to suggest the dual diagnosis. Our problem in the matter of associated carcinoma of the lung and pulmonary tuberculosis is the same as that in uncomplicated pulmonary neoplasm, namely to discover the presence of cancer of the lung before it has become inoperable. This is obviously much more difficult when the situation is obscured by the presence of pulmonary tuberculosis. Nevertheless, as pointed out above, it is equally important, because pulmonary tuberculosis is not likely nowadays to cause death, while the proportion of patients who recover from pulmonary malignancy is disappointingly small.

In some of the case reports presented here, and in many of those appearing in the literature, the diagnosis of pulmonary malignancy was suspected only because patients failed to improve after antimicrobial therapy for tuberculosis. In our opinion, this criterion should be dismissed as an unsatisfactory guide to the diagnosis of supervening carcinoma of the lung in a patient already suffering from pulmonary tuberculosis. It is quite clear that, by the time the chest physician has become dissatisfied with the clinical and roentgenological progress of his patient with pulmonary tuberculosis, and begins to suspect tumour as well, the growth has probably progressed beyond the point of surgical attack.

It is our impression also that most of the distinguishing features, suggested in the literature as being of value in the diagnosis of combined tuberculosis and neoplasm, are of no assistance in the *early* detection of the dual condition. Clinically, the presence of wheezing, loss of

weight, weakness, hæmoptysis and dyspnœa, while of importance in indicating the presence of uncomplicated pulmonary malignancy, is of little or no value in arriving at a diagnosis of carcinoma of the lung when pulmonary tuberculosis is already present. From a roentgenological standpoint, the diagnosis of hilar prominence, paratracheal lymph node enlargement and atelectasis, all suffer from the same lack of specificity. It is possible that the presence of articular disturbances, such as hypertrophic pulmonary osteoarthropathy, which have been reported by some authors[8-10] as being of assistance in the diagnosis of pulmonary neoplasm, may lead to its earlier detection in patients who already suffer from pulmonary tuberculosis. In our very small series of cases, no such early manifestations were noted.

It would seem, at least from our own experience, that the clues which may lead to the early diagnosis of combined pulmonary tuberculosis and carcinoma are of a very general and in fact tenuous nature; but, for what they are worth, they should perhaps be described. Firstly, the patient's age and sex appear to be of basic importance. It is our opinion that the possibility of carcinoma of the lung should always be suspected when a male patient over the age of 40, with undiagnosed pulmonary disease, presents himself for assessment, even though evidence of pulmonary tuberculosis is subsequently discovered. Secondly, the presence of a rounded, circumscribed pulmonary density, found in a roentgenogram, preferably at a site removed from that of the previously known tuberculous lesion, should lead one to carry out further investigations with the possibility of a supervening pulmonary malignancy in view. This is considered to be of some importance, despite the fact that the so-called tuberculoma is a not uncommon finding in pulmonary tuberculosis. And finally, as in all such situations, a high "index of suspicion" will be of infinite value in ensuring that the diagnosis of combined disease will be less frequently missed in the future. After all, a diagnosis of coexistent pulmonary tuberculosis and malignancy is not likely to be entertained if the combination is not known to constitute a well-documented clinical entity.

SUMMARY

Five cases of associated pulmonary tuberculosis and malignancy are reported and described in detail.

In two of these cases, the dual diagnosis was suspected before surgery or necropsy. In another two, the simultaneous occurrence of the two conditions was completely unsuspected, and was an incidental post-mortem finding. In the fifth case, uncomplicated pulmonary malignancy was suspected before surgery, while both pulmonary tuberculosis and carcinoma were discovered at thoracotomy.

Two of these patients are still alive and well, three years and two years after surgery.

The possible features by virtue of which the co-existence of these two conditions may be suspected are discussed; and a plea is made for a higher index of suspicion as an aid in the diagnosis of such combined lesions.

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INVOLVEMENT OF THE THORACIC WALL IN BRONCHOGENIC CARCINOMA

Gronqvist of the Mayo Clinic (*Proc. Staff Meet. Mayo Clin.*, 33: 487, 1957) made a study of 16 cases of bronchogenic carcinoma in which the thoracic wall was involved. Pneumonectomy was performed in seven instances and lobectomy in nine. The involved part of the thoracic wall was removed simultaneously in all cases. The most prominent symptom was pain in the thoracic wall. No cases of Pancoast's syndrome were present in this series.

Six of the 16 tumours were grade 4 squamous-cell carcinomas, six were large-cell undifferentiated carcinomas and four were high-grade adenocarcinomas. The intercostal muscle bundles and the structures in them were invaded in all but three instances.

Follow-up data were obtained in all cases. Ten patients have died from their disease. Two of the six surviving patients have lived more than two years (2-1/3 years and 6½ years, respectively) after operation. The carcinoma did not extend into the intercostal muscle bundles in either of these two patients. The third patient, who had involvement of the parietal pleura only, was living 13 months after operation.

This study suggests that either pneumonectomy or lobectomy in association with resection of the thoracic wall for bronchogenic carcinoma can be a curative procedure if the involvement of the thoracic wall is limited to the parietal pleura.

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SOLITARY EOSINOPHILIC GRANULOMA OF SKULL (1950); OSTEOCHONDRITIS DISSECANS OF KNEE (1954)

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IN JUNE 1950 a solitary eosinophilic granuloma developed in the skull of a seven-year-old girl, the diagnosis being confirmed by pathological section. Following incision and biopsy the lesion healed uneventfully in a few weeks, and the child was well until May 1954, when she appeared again with a painful knee. Radiographs revealed the presence of a typical lesion of osteochondritis dissecans of the medial condyle of the right femur. The child was treated conservatively and the lesion was healed within a year. There has been no recurrence of either lesion.

HISTORY

The child was seen first on June 15, 1950, with the complaint that she had a tender spot on the back of her head. On enquiry, the mother stated that the child had bumped her head two years earlier but had not complained of it since the original injury. She had also had a sharp tap on the head with a ruler two weeks before tenderness developed.

On examination, the child appeared normal in physical and mental development, and there was no sign of injury except for a small area of tenderness in the occipital area. She was sent away with the thought that this was a minimal injury in which the tenderness had persisted, but she came back in a week with a painful swelling in the area, tender and slightly fluctuant. At this time, nits were found in the hair, and a diagnosis of suppurative cellulitis of the scalp was made. Temperature and pulse were normal. The patient was admitted for incision and drainage.

Under general anæsthesia, a vertical incision was made through skin, and continued through aponeurosis when no pus was encountered. This incision was continued until a thin serous exudate was obtained, and was then spread with blunt forceps, the points of which touched bare bone. A culture of the fluid was taken and a piece of tissue removed for biopsy. The incision was allowed to fall together without sutures or drainage, and a dressing applied. A skull radiograph showed a circular defect through both tables of the occiput, the defect being about one inch (2.5 cm.) in diameter (Fig. 1). The tuberculin test was known to be negative from a previous routine school examination, and the Wassermann reaction of both parents was also known to be negative. In a few days the report on the culture came back—"no growth"; and in a few more days the pathological report was received, with the diagnosis: "chronic inflammatory reaction in infected tissue." The patient was given penicillin, 400,000 units per day, postoperatively. Her temperature did not rise above 100° F. and she had no further pain after the operation. She was happy, but the diagnosis was not yet established.

The radiographs were sent to a neurosurgeon, who asked that the pathological sections be sent to the Department of Pathology at the University of Toronto. After review of the sections, all pathologists concerned concurred in the final histological diagnosis of eosinophilic granuloma. The final pathological report reads: "Microscopic report: The material submitted consists of a rather scanty amount of delicate fibrous tissue throughout which there is a recent hæmorrhage. Numerous thin-walled blood vessels are present. A marked feature is a proliferation of reticulo-endothelial cells associated with numerous polymorphonuclear leukocytes and a considerable number of eosinophils. The latter are not as abundant as is usual in eosinophilic granuloma but the appearance is essentially one of that condition. The occasional large histiocyte is noted. Diagnosis: eosinophilic granuloma."

By the time the diagnosis was established, the skin incision was healed, and the skull defect was closing rapidly (Fig. 2). It continued to close uneventfully. Radiographs three years later (Fig. 3) showed the new bone still visible in the skull as an area of increased calcification. At that time there were no signs of lesions in long bones, chest, pelvis or back, and no bone lesion in either knee.

The patient was next seen May 13, 1954, now 11 years old. The complaint at this time was an ache behind the right knee, of about a week's duration. The parents had noticed a slight limp for a few days. The only injury they could remember was a fall about one year previously, which had caused a small cut over her patella. The fall had caused no immediate signs or symptoms except those of a mild contusion-abrasion at the time of the accident.

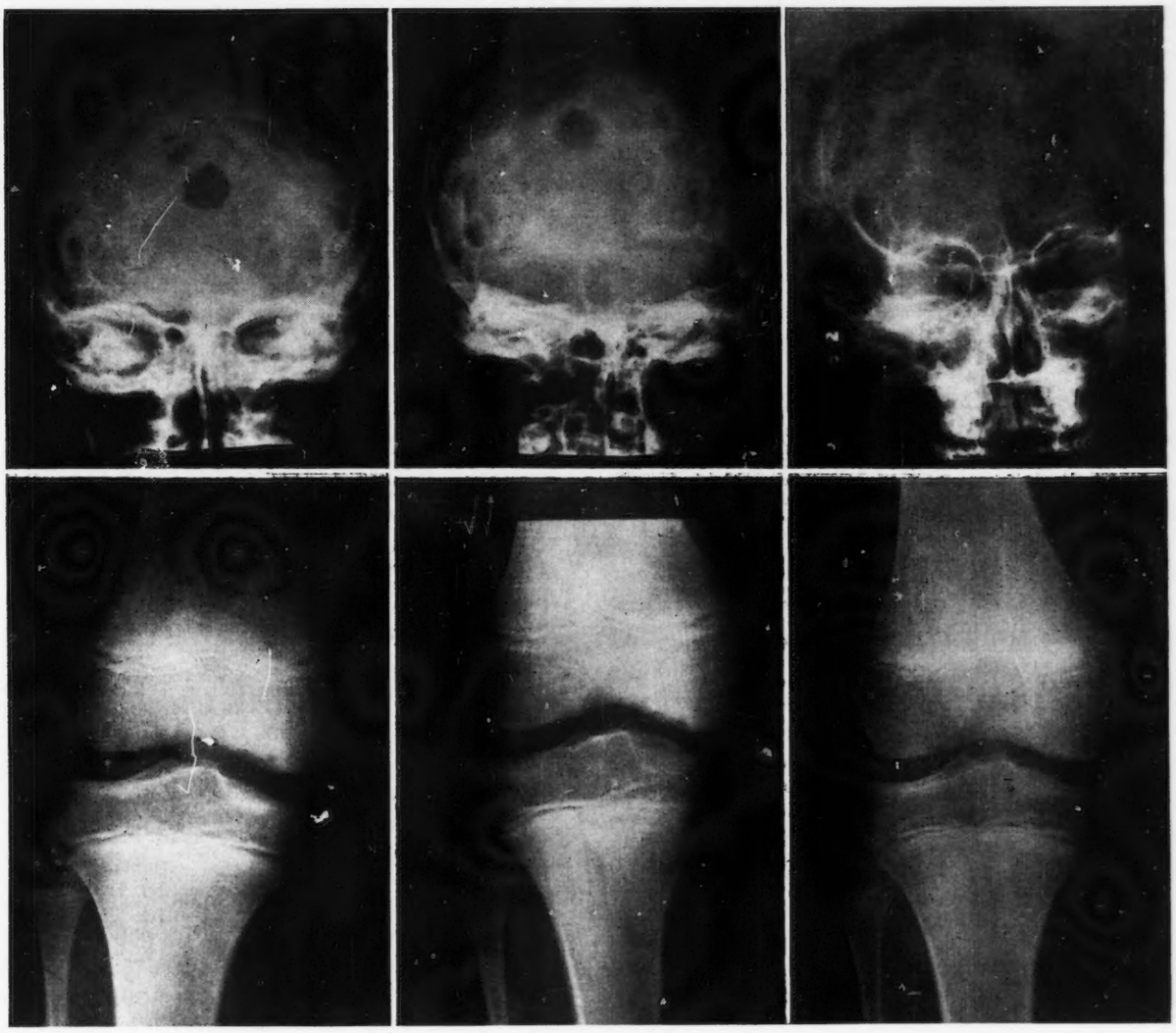
The child walked with a distinct limp. There was a full range of movement in the knee, no demonstrable excess of synovial fluid, and no wasting of quadriceps. Radiographs of the knee, however, showed a lesion on the articular surface of the internal condyle of femur at the junction of the posterior third with the anterior two-thirds at the intercondylar notch (Fig. 4). And those taken at an exact tangent 10 days later showed a flake of bone 1/3 inch in diameter, of increased density, apparently not yet separated from its bed. The bone subjacent to the flake was rarefied but this rarefaction was within an area of sclerosis, creating the appearance of a flake within a crater (Fig. 5).

A diagnosis of osteochondritis dissecans was made and, as it was considered that the fragment was not yet completely separated, the knee was immobilized in a position just short of full extension by a plaster which extended from upper thigh to ankle. The child was allowed to walk, as there would be no direct pressure on the affected area with the knee in this position. She did not miss any school throughout her illness.

There was immediate relief from pain, and in three months there was a distinct improvement in the radiological appearance of the lesion. The base of the crater was less dense, and the flake of bone was not visible. Immobilization was continued for another six weeks, after which the plaster was removed and replaced by a crepe bandage. By the middle of November 1954, the child walked without a limp, and though there was slight irregularity of the articular surface of the affected area, the crater had disappeared (Fig. 6). On April 28, 1955, there were no signs of abnormality of the knee, and the radiograph was normal. Thus, within a year, the lesion was healed clinically and radiologically, and the child had suffered no discomfort after the application of the first cast.

DISCUSSION

The condition known as eosinophilic granuloma of bone was so named in 1940 by Lichtenstein and Jaffe, who subsequently in 1944 published another paper[1] describing it as "a condition affecting one, several, or many bones but



Top—Figs. 1, 2, 3
Below—Figs. 4, 5, 6

Fig. 1.—Eosinophilic granuloma. Early stage showing clearly demarcated margins of bone defect. **Fig. 2.**—Healing lesion, eosinophilic granuloma. **Fig. 3.**—Healed lesion, eosinophilic granuloma. Excess calcium deposit in newly laid down bone. **Fig. 4.**—Osteochondritis dissecans —early. **Fig. 5.**—Osteochondritis dissecans—early. Tangential view, showing partially separated calcified flake. **Fig. 6.**—Osteochondritis dissecans. Lesion almost healed radiologically.

apparently limited to the skeleton, and representing the mildest clinical expression of the peculiar inflammatory histiocytosis also underlying Letterer-Siwe disease and Schüller-Christian disease."

Since then other cases have been recorded and described. The disease is usually found in children and young adults of either sex; the lesion is usually solitary, and is seen in the bones of skull, chest, back or in the long bones of the extremities, but it is not uncommon to find multiple lesions of bones, and, rarely, extraosseous granulomata may accompany the bone lesion. One case has been reported with associated diabetes insipidus, tending to link the conditions more strongly with Schüller-Christian disease.

The most common local signs and symptoms are local pain, tenderness, and swelling. Secondary local signs and symptoms depend on the site of the lesion. Local tenderness without pain is the most common early complaint. The lesion may be asymptomatic; when lesions are multiple one may produce symptoms and the others none. There may or may not be leukocytosis. In some cases, whether or not there is leukocytosis, the differential count shows a slight increase in eosinophils. Blood calcium, phosphorus and cholesterol levels have been consistently normal. Tissue studies for bacteria and virus cultures have all been negative.

In an early phase, the tissue from a lesion is described by Lichtenstein and Jaffe as likely to

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be more or less hæmorrhagic and cystic, and to show a relatively small amount of soft brown granulation tissue which may be streaked with yellow. These authors describe the non-necrotic material as presenting, on microscopic examination, conspicuous sheet-like collections of large phagocytic cells of the nature of histiocytes, interspersed among which are more or less conspicuous numbers of eosinophilic cells and especially eosinophilic leukocytes. One finds actively phagocytic multinuclear giant cells, especially in the vicinity of fields of hæmorrhage and necrosis. Histiocytes constitute the basic component of the lesion, being apparently derived from the multipotent reticulum cells in the adventitia of the blood vessels in the marrow. In some lesions or parts of lesions one may also find lymphocytes, plasma cells or even neutrophilic polymorphonuclear leukocytes in small numbers. Lichtenstein and Jaffe point out that the granulation tissue present in early stages of destructive skeletal lesions of Letterer-Siwe disease may be indistinguishable microscopically from such tissue in corresponding lesions of eosinophilic granuloma of bone.

Most writers believe that this reaction of the reticulo-endothelial system is due to infection. Jaffe and Lichtenstein suggest that the portal of entry may be the gastro-intestinal tract. Trauma is rarely considered as an etiological factor, and is not mentioned in most case reports.

The two most commonly used forms of treatment are curettage and roentgenotherapy. A biopsy at least is considered necessary to establish the diagnosis, and so it is not possible to prove that a solitary lesion of established diagnosis has healed spontaneously. However, in multiple lesions in which the diagnosis is made on the basis of curettings from one lesion, the remainder may heal in variable time, with or without roentgenotherapy.

Osteochondritis dissecans in children is a very rare condition. Green and Banks,[8] who published an excellent paper on the subject in 1953, were able to find only nine cases reported in children prior to their own paper, in which 27 patients, all treated at the Children's Hospital, Boston, in the previous 12 years, were studied.

Most of the patients have only one joint affected but Green and Banks reported that eight of their patients had more than one joint involved and in most of these the lesions were bilaterally symmetrical. Six of their patients showed osteochondritic lesions of the ordinary type in other areas, three of these being Osgood-Schlatter type lesions, two having osteochondritic lesions of the spine and one having osteochondritis of the lower pole of the patella.

Green and Banks draw attention to the significance of multiple lesions associated with osteochondritis of other types, in discussing etiology. Trauma has usually been cited as a causative factor, but the occurrence of multiple lesions and the frequent association with osteochondritis of other types suggest some other factor which, in the opinion of these authors, makes the individual particularly susceptible to osteochondritis dissecans and to osteochondritis in general.

In 1944 Strange[9] reported a case of osteochondritis dissecans in a four-year-old child. He immobilized the knee six weeks and prevented weight-bearing, and in a few months a complete cure was obtained.

Green and Banks treated 25 of the 36 joints in their cases without surgery; three which they treated by protection were first opened and the lesion left untouched. Their reasoning is that in osteochondritis dissecans in children, something causes the subchondral bone and the bone immediately subjacent to die. The cartilage in the beginning remains healthy since its nutrition is derived from the synovial fluid. From this point, the clinical course is variable. The cartilage may crack and be extruded into the joint, together with the involved subjacent bone, or, if the joint is protected, the dead bone may be invaded and the lesion may heal by "creeping" substitution.

CONCLUSION

A solitary eosinophilic granuloma of the skull in a girl seven years of age was followed, four years later, by osteochondritis dissecans of the femur. No conclusions can be drawn and no theories can be developed, but the occurrence of these rare conditions in one child suggests the possibility of some unknown common factor in the two diseases.

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Special Article

IN QUEST OF OBSCURITIES IN BACTERIAL INFECTIONS*

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ON READING THE TITLE of this address, I believe there are very few who would ask: what need is there to search for obscurities in a subject that is all obscure? It is probable that an appreciation of the stupendous advance during the past century in the prevention and treatment of bacterial infections would prompt the opinion that the present obscurities are merely a matter of technical minutiæ, to expand the established principles which have been proved by results. But I have an inkling that the one extreme is almost as bad as the other, for, although hopeless inertia makes no progress, complacency restricts imaginative endeavour, and the cardinal feature of great research is the recognition of fresh determining principles which all at once reorganize our thought, method and purpose.

We have learned to find, name and classify bacteria, distinguishing those connected with disease and associating recognized kinds with diagnostic clinical manifestations of illness. So we are encouraged to speak confidently of knowing the cause of specified diseases. We have demonstrated that some kinds of bacteria are invasive and others not, that some produce toxins, some can develop means of resisting phagocytosis or otherwise compete against the host's mechanisms of defence; we recognize regional localizations and tissue or cell predilections; we have traced the sources and the routes of spread of bacteria by fomites, water, food and arthropod vectors, and we have established the applications of hygiene. So we rather boldly claim to understand how bacteria cause disease.

We have discovered how to interfere with various of these bacterial activities by specific active and passive immunization, for both prophylactic and therapeutic purposes; and we have gained confidence in passing from simple chemical disinfectant procedures to the use of selective antibacterial agents of spectacular therapeutic power. All this with little more than a very faint glimmer of understanding of the vital processes involved, but we are versed in treatments based on dosage, we are emboldened by the availability of another antibiotic should one fail our need and the hope that yet others will be found. So, with the justification of unprecedented cures, we hopefully anticipate that we are on the verge of the control of infectious diseases.

It is not my purpose to belittle the knowledge science has gained of infectious diseases, nor would I in any way deplore the clinical applications of it, for I believe there is no other branch of learning that equals what this knowledge has provided for human good. But what I would do is provoke a scrutiny of what we do not know. If we consider figuratively that the vast store of factual information on infectious diseases forms a pattern, let us, as it were, survey the gaps in the design rather than its decorative form; not so much to learn from their edges where little pieces can be attached as to get a perception of where we lack an essential understanding.

This is no easy undertaking, for some defects are no doubt small and hard to see, but by the very break they cause they prevent the linking of great features; while others may be too large to comprehend until some means for their detection is developed. Perhaps our greatest handicap lies in our setting for ourselves limiting prejudices and preconceived theories, or even superstitions.

Something of the trouble I feel on this score is expressed in a scholar's translation of a phrase written by Boethius in about A.D. 524, which says:

> "How shall he follow the unknown?
> How shall he find it, and when found
> How shall he know it? . . . "

Everything points to this being a difficult approach to the improvement of our knowledge. It is admittedly much easier, and far more comforting, to list a series of successes, especially when the results conform to what is accepted as desirable, than it is to embark on uncertain ventures of doubtful outcome and perhaps disrupting consequence. But surely there is excitement in getting into difficulties and how else are we to fathom the unknown? "Only

*From the Department of Medical Research, University of Western Ontario. An address to the Academy of Medicine, Toronto, November 6, 1956.

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by experience and taking risks. That is how everything worth while is learned."

I find it a disturbing reflection that Burnet should thoughtfully observe, in his book *Natural History of Infectious Disease* in 1953, that "The advances of the last twenty years have not been so much in the understanding of the processes of infectious disease as in the provision of agents of extraordinary efficiency for dealing with its practical problems." It is also noticeable that, in recent symposia concerned with cellular metabolism in bacteria and their hosts and in experimental animals, the chief interest seems to be in differences that might explain the action of antibiotics and illuminate the development of resistant strains of bacteria, or indicate a "lead" to "a rational chemotherapy". Of themselves the reported findings are extremely interesting, but their trend emphasizes Burnet's observation and strongly supports a plea for a more enlightening concept of the nature of the essential problems in infectious disease.

Therefore it may prove interesting to try to recognize some examples of unexplained features of infections and see where they may lead us, both in the formulation of research problems and in reflections without restriction to utility. Quite evidently this process requires the combination of interests of both the clinical and the laboratory workers to gain a full advantage. However, it can be applied within the limited range of individual experience, which I now propose to do, hoping for a good measure of indulgence since having committed myself I must "make a virtue of necessity".

The cause of infectious disease might not at first seem open to question. On general principles of etiology everyone must accept the causative role of *Salmonella typhosa* in typhoid fever, *Mycobacterium tuberculosis* in tuberculosis, and a long list of similar proven examples; for the characteristic disease is not manifest in the absence of the identifiable micro-organism. Although there are diseases, such as gonorrhœa, in which there is always some measure of a pathological state wherever the specific organism is found, there are, too, many instances when no sign of disease develops in the presence of organisms of established pathogenicity. This in its variations leaves us wondering. For want of precise knowledge, we are prone to blunt our curiosity by explaining the situation in terms of variation in virulence, susceptibility and resistance, pathogenicity, invasiveness, communicability or degrees of immunity. Many of these terms lack precise meaning and most of them involve a complexity of interacting factors, some of which I have discussed elsewhere. But even more important than their failure to explain the situation adequately is that their careless use may mask or disguise the very problem we should keep clearly before us. It is perfectly true that influences contributing to the states implied by bacterial virulence, by host susceptibility and resistance, by invasiveness and pathogenicity, play their part in the development of the diseased condition, but to be helpful in understanding of the cause of disease the elements constituting these complexities need to be separated and understood.

For example, the virulence of the pneumococcus, which is easily increased by animal passage and is measurable in terms of the size of the dose which is fatal to a mouse, resolves into the development of a capsule which in turn allows of resistance to phagocytosis. But this cannot be the whole story of the development of the symptomatology and pathology in pneumonia or explain its fatality. It is unlikely that mere numbers of free bacterial cells are responsible, since great numbers of avirulent cells are tolerated. It is possible the capsular material plays other parts, and its importance is indicated by the therapeutic and protective action of immune serum. The character of the lesion and the complete restoration of the lung on recovery are not explained by the mere presence of large numbers of pneumococci, and there is room for further investigation of the cause of death beyond the observation of a frequent persistence of a positive blood culture in fatal cases.

Virulence is not displayed in identical fashion by all different species of bacteria. Despite an indication of phagocytosis contributing to resistance to the meningococcus, its virulence seems not to depend principally on evading ingestion. Also there is not a striking augmentation of capsule with virulence, and agglutination titre is not a measure of therapeutic value for meningococcus antiserum. Virulence of the meningococcus is not readily raised by animal passage as with the pneumococcus, but cultures treated with suitable lytic extracts of polymorphonuclear leukocytes increase their infectivity. It seems that meningococcus virulence is displayed particu-

larly as intracellular survival with a capacity to destroy the leukocyte. Perhaps there may be an element of cell invasion rather than phagocytosis, and even at the time Weichselbaum discovered this organism its intracellular habit was remarked. Such a special capability may have wider implications in the pathology of this disease than we have realized, and the character and range of its effect on intracellular host physiology is completely unknown.

These are but two examples of differing involvements of what are only part of the complexity the term virulence comprehends. But, without a more searching analysis of the influences contributed by both host and parasite, the invocation of virulence to explain clinical and epidemiological features of infectious disease seems to me unsatisfactory. Outbreaks seem to be characterized at times by epidemic strains, but whether this is a matter of virulence, or of a regionally new antigenic type, or a matter of mass opportunity is seldom clear.

It is quite possible that circumstances may occasion altered host physiology to be a determining influence, perhaps allowing development of intrinsic bacterial factors, perhaps changing the balances which control host susceptibility and resistance. That these can occur is indicated by the isolation of plague bacillus strains of lowered infectivity at the tail end of an epidemic, and by the fact that purine-requiring typhoid strains are not infective to mice intraperitoneally unless something like adenine is given at the same time. The situation must not be confused with epidemiological features determining opportunity, such as overcrowding, ventilation, vectors, etc. The study that is required relates to the influence of general and regional metabolism on liability to infection. With all the studies of metabolism and physiology in both mammals and bacteria, extremely little has been contributed to elucidate the processes of infection.

When it is said that *Corynebacterium diphtheriæ* causes diphtheria by virtue of the toxin it produces, which, in part, acts by blocking the synthesis of cytochrome components, then an approximation is being made to the proper description of the cause of diphtheria. It is still incomplete and can be elaborated by the conditions of production of toxin, the chemical and physical characterization of the highly purified toxin, and details of its interference with the intracellular respiratory systems. There are to be added, too, the other antigenically distinct toxin components, such as the neurotoxin (Ehrlich's Toxone) responsible for the late development of paralyses. However complete the description of the toxin can be made, and its exact interaction with vital processes of cells elucidated, this alone does not describe the causation of diphtheria. There are still required the processes of localization of the bacillus in the body and its competition with host defence mechanisms, the incubation period, the process of absorption of the toxin and its distribution and penetration of susceptible cells with the reasons for their susceptibility, and the derangement of the physiological processes of the whole patient as primary or secondary consequences of the direct action of the toxin. For diphtheria is a state of illness of the entire patient, and death may well depend on the secondary effects, however essential the primary action of the toxin actually is.

Even though this attempt at a comprehensive view of the cause of diphtheria is incomplete, it does bring into relief that the gaps in our knowledge relate to almost everything that has been listed. The identification of *Corynebacterium diphtheriæ* and a fraction of the characterization of its toxin, together with a part of the action of the toxin on vital intracellular processes of the body, are the only definite causal factors for which we can claim an encouraging measure of understanding.

The problems to be solved are not confined to bacteriology, although there remain evident needs in that domain. For, besides the involvement of physiology, pathology and biochemistry, there is urgent need for clinical interest beyond the routine of diagnosis and empirical treatment. However, real advances will only come through co-operation between these various interests, promoted by mutual understanding and pooling of facilities.

Quite evidently such a comprehensive review of the cause of a disease is inconveniently cumbersome, but any attempt to categorize it must not lose sight of the ramifications of primary effects and of the contributory influences of disturbances of host physiology. Otherwise, essential problems will not be kept prominently in view, and the all-important clear recognition of what we do not know will be wanting as an urge to investigation.

No one can gainsay the astonishing therapeutic advantages brought to the sick by the

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discovery of sulfonamides and antibiotics. But, while acknowledging this fully, I believe there is a very much greater significance to medicine from the understanding we shall gain of the processes of infectious disease growing out of the study of the ways these drugs produce their effects.

The concept of competitive antagonism by analogues of metabolites has initiated comparisons of the substrates and products of enzyme activity between host cells and parasites. To a large extent, at first, many workers designed their investigations to discover such distinctions as would result in therapeutically ideal antimetabolites. Although this has not been outstandingly productive of valuable chemotherapeutic agents, there is accumulating an extensively varied mass of detailed knowledge of cellular metabolism, especially of bacterial cells. It has revealed many complications in the requirements for active therapeutic agents and many diversities in the pathways for biosynthesis of essential substances. It has demonstrated selective utilization of metabolites and analogues, and limitations due to the delicate adjustments of identical processes as exhibited in the parasites and in the normal and abnormal cells of the host. Even though the initial purposes may not have been attained, there is emerging an appreciation of new intricacies in the processes of infections that promises revealing developments.

The hoped-for distinctive biochemical character to mark bacteria has not been widely demonstrated. Furthermore, Dubos finds it pertinent to ask "not why pathogens can cause disease, but rather why saphrophytes do not proliferate as well as pathogens—or at all—*in vivo*". There have been found certain intermediates in carbohydrate metabolism of some bacteria, even pathogens, to which animal cells are impermeable. There are at present few identified chemical peculiarities of bacteria; diaminopemilic acid is not shared with bacteria by any organism other than blue-green algæ, which some think really are bacteria, and hydroxymethyl cytosine is peculiar to a bacteriophage. Other than the competition between sulfonamides and para-aminobenzoic acid, the therapeutically useful antimetabolites depend upon quantitative rather than qualitative relations. Much interest has focused on the strange assortment of interferences by analogues and their limitations in both bacterial and host cell metabolism.

It is beyond my scope to detail any of these but their intermingling should be noticed, in order to demonstrate the difficulty of segregating problems as purely bacteriological, physiological or clinical in considering disease. It also supports my thesis that identifying the cause of infectious disease is not confined to the mere identification of the initiatory pathogen. Thus, the involvement of derivatives of folic acid in hæmatopoiesis spread to their functions in abnormal cells in leukæmia and their biosynthesis by different species of bacteria. The chemotherapeutic use of analogues brought out the delicate balance limiting attainable inhibition of abnormal cells and damage to normal cellular activity. There also appeared marked development of resistance to these analogues, and even dependence, not only in strains of bacteria but in experimental animals and patients. Then, arising out of Hitchings's studies of bacterial requirements, the antagonistic interactions were discovered between derivatives in the "folic acid series" and derivatives of antimalarial drugs of the "Paludrine series", and so on to mercaptopurine in a similar way.

Bacteriological studies may therefore be expected to contribute even more in the future than they have in the past, and that not confined to the processes of infectious diseases. But their significance will largely depend on integration with studies in other fields. For this reason, as well as the undiminished seriousness of bacterial infections, there is need for the enlargement of departments of bacteriology and the encouragement of highly trained workers. Not that there are natural boundaries separating branches of science, but the exigencies of specialized techniques based on intimate knowledge, the vast expansion of the literature and the development of technical language require specialization to secure effectiveness.

There is a renewal of interest in the mediators of infection, involving susceptibility and resistance, in the activation of latent infections and in tolerance of parasitism. Some investigations probe constitutional and hereditary characters, chiefly of physiological and biochemical nature, and these are tested by incubation times and survival times following infection. Others are

concerned with nutritional and metabolic studies, hormonal disturbances, and irradiations, in relation to establishment and progress of infection. The influence of mucins, polysaccharides and of new-found proteins in plasma, cells and tissues, has promoted experiments variously contrived to give information in terms of lethality, but also, according to their nature, on bacterial localization and dispersion and proliferation, on the permeability of capillaries and membranes, and on phagocytosis.

There may yet be disclosed an extension of the concept of "*lethal synthesis*" to the products of pathogenic bacteria and it might well prove to be revolutionary in both the elucidation of some processes of infectious disease and its rational treatment. This concept arises from R. A. Peters's investigation of Gifblaar poisoning in South Africa, which misdirects intracellular enzyme action to the synthesis of a fatally damaging inhibitor from innocuous metabolites. This is not too far-fetched when the altered appearance of mitochondria brought about immediately by staphylococcus toxin is remembered, and because certain enzymes are organized in mitochondria.

From the investigations underlying these and various other considerations, there has arisen a quite natural use in the literature of a new idea which is referred to as a *biochemical lesion*. This is not an evasive explaining away of obscurities, but a verifiable situation of remarkable potentiality. Biochemical lesions are claiming a place in cellular pathology, and, when reading G. R. Cameron's elucidation of cloudy swelling, one wonders whether nephrosis caused by *Streptococcus pyogenes* Type 12, studied by R. W. Reed, might not fall into this category.

There are numerous examples in pathogenic bacteriology when the most abundant presence of bacteria seems insufficient explanation of the resulting disease. Carrier states, subclinical infections and the ineffectual though beneficial multiplication in the tissues of attenuated strains used for living vaccines (smallpox, yellow fever, BCG, plague and Pasteur's anthrax vaccine, to name a few) are indicative of unsolved problems. The question is complicated by the effects of tissue environment, organotropisms, rate of multiplication, host constitution and state of metabolism, immunity, as well as what is meant by the term virulence. But even if these instances are set aside as special cases, and if attention is confined to declared characteristic disease, something other than the mere number of bacteria determines the situation. That the species of bacterium is associated with the clinical character of the illness proves the general statement and in several instances specific toxins are proven determinants; also direct action of other products and properties of bacteria may be invoked as influential. But, granting that these findings have been applied for the diagnosis, treatment and prevention of disease with most satisfactory results, there is still much that needs to be gained.

Several known infections are peculiarly human, others peculiar to other species, and these restrictions of susceptibility and resistance must involve environmental requirements of the parasite that are provided by the host. But to some extent, the characters of the disease must be determined by special responses of the host to special secretions, metabolites and even deprivations which surely pertain to the pathogen. The interactions so provoked may result in deflections or perversions of host enzymatic processes to provide a variety of secondary biochemical lesions, which must vary in manifestations and could be of any degree of seriousness up to lethality.

I wish to declare most emphatically that this very definite circumstance is entirely opposed to the tenets of so-called "stress". "Stress" requires essentially that "there must be in the body some mechanism through which all types of injuries are met in the same way", and this is declared to be "the general adaptation syndrome". I defy anyone to distort the responses and processes of bacterial infections to conform to the interpretations of "stress". "Don't let us make imaginary evils, when we know we have so many real ones to encounter."

A peculiarly human disease that these reflections call to mind is cholera. This may seem a remote disease, only having visited Canada in 1832, 1849 and 1866 (not in 1873, though then in the United States), but those who have seen cholera will have retained a forceful impression of urgent bacteriological and clinical difficulties amounting to mysteries. I wish to use only one of these as illustrative of my theme.

The profuse diarrhœa and vomiting produce an extremity of desiccation and loss of electrolytes, which with suppression of urine can be held accountable for much the patient suffers.

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There is a tarry concentration of the blood, which will not clot and often will hardly flow; it becomes acid and oxygenation of the hæmoglobin in distorted corpuscles is impaired. But the pointer to which I wish to draw attention is the loss of proteins from the plasma. The stools become alkaline and contain detectable "albumin" and appreciable quantities of phosphates and chlorides. In fatal cases the blood accumulates in the visceral veins while the vessels elsewhere are nearly empty. It is also interesting that in the reaction stage, or in early convalescence, there is often œdema which lasts two to ten days, and disappears suddenly and is thought not to be due to heart or kidney conditions. During the severity of the disease, especially in the algid stage, absorption from the gut is lost; so much so that not only are nutrients and salines not absorbed but also medicaments can remain to accumulate. In the days when opium was given to cholera cases, there have been instances during the reaction stage of fatal poisoning by the accumulated opium when absorption was re-established. It is a much debated point whether desquamation of the mucosa of the small intestine is an *in vivo* lesion or only takes place post mortem.

The essential features of this excerpt from the complexity of cholera seem to me only explicable on the basis of enormously increased vascular permeability to salts, proteins and fluids; but the transudate is not retained in the tissues and passes through the mucosa into the lumen of the small intestine. It is not simply a leakage, for absorption from the gut is greatly impaired. It seems most likely that the alteration to the permeability barriers is effected by a product of the cholera vibrio, which itself does not invade the tissues of the body. That a toxin is absorbed from the gut, where it is produced, is in itself extraordinary in view of the impaired absorption of nutritives, salines and drugs in cholera. A toxin has been presupposed ever since the work of Koch in 1883, and the energy of many investigators has been expended, with violence and strong chemicals, without yet discovering it; an effort out of all proportion to the ready ease with which it is produced by the vibrio in the cholera patient.

The search for the cholera toxin is impeded by the lack of a susceptible experimental animal. Tests for activity which depend on measurement of a lethal dose seem to me inappropriate and most likely to miss their purpose. It is thus not surprising that an acceptable toxin has not been found and that specific antisera have not proved encouraging in treatment of cases. It is true that toxic substances, described both as endotoxins and exotoxins, have been extracted from cultures, and in a recent review Pollitzer has devoted some 18 pages of print to them. But the problem remains unsolved. There is, however, a most pertinent experimental observation by Burrows and his colleagues. They found that living vibrios, or crude toxin preparations, increased the flow of Ringer-Locke solution through living semipermeable membranes by two to six times the normal rate. With thorough washing the flow rate returned to normal.

The supposition that permeability derangements could determine the main features of the cholera state immediately allows speculative consideration of bacterial polysaccharides, mucins and the activation of certain plasma globulins as active participants. Bacterial levans have been shown to prevent penetration of antitoxin and dyes into tissue sites and bacterial polysaccharide possibly joins in promoting capillary permeability, also mucins are used to enhance infection. So it would seem worth testing what effects of this kind the polysaccharides and glucolipoids present in the cholera vibrio might exhibit. Miles and his colleagues have demonstrated globulins in plasma and serum which can be activated to cause a marked increase in capillary permeability and to promote exudation. It would be interesting to know if the cholera vibrio produces substances to activate this globulin, or inactivate its natural inhibitor, and whether the development of a refractory state is prevented. Another serum component with seemingly important influences on resistance to infection is the euglobulin called "properdin" by Pillemer; it also plays a part in inactivating the third component of complement and reacts with bacterial polysaccharides and endotoxins. But this has less obvious interest in the point at issue than have the mucopolysaccharides and Miles's alpha-globulins.

Thus, in cholera, biochemical lesions may prove to dominate the processes of the disease once they have been initiated by the products of the vibrio growing in the lumen of the small intestine. The substances produced by the

vibrio which initiate and maintain these events need not necessarily of themselves be directly lethal; and the effectiveness of their activation of changes in permeability of capillaries and membranes may depend on localization at the site of absorption and production.

Another disease in which the initiating organism is confined to the lumen of the gut is bacillary dysentery, and here there is a definite toxin with selective action. The toxin has a neurotoxic element and also one which produces necrosis of the mucous membrane of the large intestine. The neurotoxin has been shown by van Heyningen and Gladstone to have resemblances in several characters to diphtheria toxins with very high potency and it may also be associated with the cytochrome system. I did a lot of work with bacillary dysentery in 1916 to 1919, which has not been published, and I wish to suggest that host excretory physiology inadvertently contributes to the character of bacillary dysentery.

I found the anti-Shiga sera I possessed would easily protect rabbits from the gut toxins, but they often died with late paralysis; they showed typical histological lesions of the motor nerve cells, without any intestinal lesions. The completely characteristic intestinal lesions were produced by whatever route the toxin was introduced, as well by injecting intact bacilli as by prepared cell free toxin. If heated at 70° C. the toxin did not produce lesions and heated bacilli absorbed all the agglutinins from the serum without altering the antitoxin activity. The toxin was completely neutralized by filtered extracts of broken-up cells of the mucous membrane of the large intestine from *normal* rabbits, but not by those of the small intestine. This toxin neutralization by mucosa cells was of the same character as antitoxin. In autopsies I have seen on dysentery cases there were, of course, extensive lesions of the large bowel, but there was commonly a general flush on the mucosa of the small intestine, especially in the ileum; but I never found necrotic lesions or a membranous exudate in the small intestine. There is quite evidently a selectiveness by Shiga toxin for cell types, but though this may be accepted for the nerve cell, does it explain the lesion in the large intestine?

In interpreting these findings to explain the gut lesions of bacillary dysentery, I do not accept the idea that the injury to the mucosa of the rectum and colon is due to the local growth and invasion of dysentery bacilli and the action of the toxin produced *in situ*. I interpret what I have described as indicating that the dysentery bacilli at first grow by preference in the small intestine; they do not much like the conditions or the company of bacteria ordinarily found in the colon and rectum. I believe the toxin is produced and absorbed in the small intestine, where the mucosa does not produce a natural neutralizer of the toxin, as is found in the colon. This diffuse absorption does no very evident damage. I believe the Shiga toxin is *excreted* by the mucous membrane of the large bowel and in its concentration it overcomes the neutralizing agent in the mucosa and causes the necrotic lesion, with its distribution over the entire surface of the large intestine mucosa.

Thus, although the direct cause of the gut lesion in bacillary dysentery is the toxin, it would appear that the site and limitation of the lesion is due to the excretory function of the large bowel. It seems probable that the injury is a direct action of concentrated toxin, but how it is effected in terms of cell function remains a mystery. It is curious that this excretory possibility is overlooked in various other forms of colitis; when we fail to find recognized pathogens in examinations of the stool, it is possible that toxin producers should be sought elsewhere in the body. It is also probable that the excretory process is accompanied by a biochemical lesion, just as that seems possible in nephrosis, and the activating agent might be restricted by regional physiological functions or availability of localized enzyme systems.

This disquisition attempts to indicate a method of finding and knowing the gaps in our knowledge of infectious disease, which is necessarily the first step in gaining an understanding of the processes involved. Emphasis is placed on the need to know exactly why a patient is ill. I have long maintained that the real work of the bacteriologist starts when the diagnosis has been made, and this must be co-ordinated with the work of his colleagues in the wards and other laboratories.

In a review on "Antimicrobial Chemotherapy", Jawetz has an interesting section under the heading "The Forgotten Host". He is concerned with the important part the patient plays in healing himself, the indications that this can be impaired by injudicious use of antibiotics and

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the omission of supporting treatment for the encouragement of the patient and aiding his natural processes. This is one of the less obvious and therefore neglected untoward effects of antibiotics. It seems to me there could be included under the same heading the oversight of the causative influences of deranged host physiology, including the biochemical lesions distinct from direct action of bacteria and their products, which contribute characteristically to the clinical form of each disease. It is probable that the secondary impairments or deflections of host physiology are often of paramount importance.

In "The Ecclesiastical History of the English Nation", the Venerable Bede relates that when John of Burgundy, Bishop of York, visited "the Monastery of the Virgins" at Wetadun, the abbess informed him that one of the virgins "having been lately bled in the arm, and whilst she was engaged in study, was seized with a sudden violent pain, which increased so that the wounded arm became worse, and so much swelled, that it could not be grasped with both hands; and thus being confined to her bed, through excess of pain, she was expected to die very soon." The bishop rebuked the abbess for "indiscretely and unskillfully" bleeding her "on the fourth day of the moon", which it may be noted was an "Egyptian day" and very dangerous. Eventually he was persuaded to say a prayer over the girl, "who lay, as I said, in great anguish, and her arm swelled so fast that there was no bending of the elbow". Soon afterwards, "the reverend Berthun, a man of undoubted veracity," rose from where they were sitting at table and visited the sick girl. He said he "perceived her countenance more cheerful and like one in perfect health". She assured him "all the pain is quite gone from my arm, where it was most intense, and from all my body, as if the bishop had carried it away with him". She called for a cup and they both drank, rejoiced by her miraculous recovery.

I recount this story to show that the tendency of modern medicine differs little in its ambition from the miraculous expectations of the seventh century A.D. The production of "miracle drugs" may be measured in tons, the cry of medicine is for new ones to replace those that are failing, the advertising rant of the drug-houses is uncontrolled, the literature is vast and largely incomprehensible, and it is abundantly clear that antibiotics are no more than a valuable adjunct in the treatment of infections.

I have drawn inferences from only a few diverse impinging observations, and though these need testing and proving, their purpose is to show that there are compelling possibilities of perhaps greater significance than the unattainable mere killing of pathogenic organisms.

Clinical and Laboratory Notes

COMPARISON OF A RAPID BLOOD SUGAR TEST (DEXTROTEST) WITH STANDARD METHODS*

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CONCEIVABLY, a simple bedside procedure for the estimation of the concentration of sugar in the blood is a desirable diagnostic aid in certain circumstances, especially when the services of a clinical laboratory are not readily available. While several so-called "rapid" blood sugar methods have been described,[1-5] apparently none has provided an entirely satisfactory combination of simplicity and accuracy. Recently, a simplified copper-reduction technique for the estimation of the blood sugar, involving a minimum of time and equipment, has been devised.§ The possible scope of usefulness of this procedure is the subject of the following report.

METHODS

The Dextrotest comprises a compact kit including a small test-tube with markings 1 and 2; another tube with a single unspecified graduation; a supply of filter cones; paired sealed tablets, one of each pair being identified as tablet "p", the other as "s", and a colour chart.

Into the narrow, graduated test-tube, water is placed to the mark "1" (2 ml.). To this is added a tablet (p) containing sulphosalicylic acid as the protein-precipitant. To this solution, whole blood (1 ml.), either oxalated or expelled directly from a syringe, is added to the mark "2". After shaking, the dark brown mixture is poured into a filter cone resting in the mouth of the other tube and the filtrate collected to the mark etched on the tube. A reagent tablet (s), composed of copper sulphate, sodium hydroxide, sodium bicarbonate and citric acid, is dropped into the filtrate. After the spontaneous boiling has ceased, the tube is shaken three or four times and,

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§Dextrotest, supplied by Ames Company, Inc., Elkhart, Indiana, U.S.A.

30 seconds later, the colour is compared with the colour scale provided: blue = 100 mg., green = 150 mg., and orange = 200 mg. %. A reading can be obtained less than five minutes after the venipuncture.

If the test indicates, or the clinical situation predicts, a blood sugar level greater than 200 mg. %, the test may be repeated or performed initially by using 2.5 ml. of water and 0.5 ml. of blood. The value read from the chart is then multiplied by two.

In order to assess the accuracy of this device, 100 unselected samples of oxalated venous whole blood with a wide range of blood sugar values were examined. In addition to being subjected to the Dextrotest, each specimen was analyzed by both the Somogyi-Nelson[6] and the Folin-Wu[7] techniques. It is generally recognized that the Somogyi-Nelson procedure yields values representing the "true glucose" content of the blood; whereas the Folin-Wu method includes the total reducing substances. Consequently, the values for the former method are lower than those for the latter. All estimations were performed in duplicate.

RESULTS

The results of the analyses are presented in Table I. The figures are the averages of the duplicate analyses by each method.

TABLE I.—COMPARISON OF BLOOD SUGAR VALUES, MG. PER 100 ML., BY DIFFERENT METHODS

Somogyi-Nelson	*Dextrotest*	*Folin-Wu*	*Somogyi-Nelson*	*Dextrotest*	*Folin-Wu*
22	100	48	110	100	177
37	100	62	113	150	142
40	100	76	115	100	134
40	100	61	118	150	164
47	100	60	118	200	156
48	100	72	119	150	142
50	100	69	122	150	194
51	100	65	126	150	155
51	100	76	128	200	163
53	100	77	134	150	173
56	100	80	135	200	166
56	100	94	136	200	174
64	100	108	136	150	170
66	100	103	138	150	162
66	100	91	138	200	210
66	100	100	147	150	190
66	100	108	148	200	183
68	100	96	150	150	213
69	100	143	151	100	197
72	100	92	154	100	182
72	100	111	155	200	185
72	100	100	156	150	195
75	100	104	160	200	200
75	100	96	160	150	198
75	100	108	163	200	218
76	100	96	164	200	208
76	100	99	169	150	188
77	150	94	172	200	202
78	150	108	184	300	253
80	100	126	184	200	246
80	100	102	186	150	212
82	100	87	188	150	206
82	200	118	190	200	247
83	100	115	193	200	244
83	100	107	197	200	246
85	100	119	200	175	236
86	150	106	202	300	284
86	100	140	203	200	240
86	100	124	210	400	239
88	100	126	214	200	295
91	150	114	219	300	256
91	100	126	222	300	311
92	100	132	230	200	269
92	100	116	232	200	294
94	100	154	238	300	310
96	100	119	240	300	311
97	100	128	243	400	278
98	100	125	270	200	334
100	150	128	314	200	371
102	150	138	460	400	490

DISCUSSION

The efficacy of the Dextrotest as a means for the estimation of blood sugar has been investigated by Davies and Paley[8] and Osborn,[9] who regard it as being helpful in medical emergencies. The present study would tend to favour their impression.

A rather serious disadvantage of the Dextrotest is that the results depend upon the visual appreciation of colours that may not match perfectly, necessitating uncertain quantitation. Gross hyperglycæmia doubtless can be detected in most instances by this method, but as a therapeutic guide for the management of diabetic patients, it may be misleading or even hazardous because of a lack of precision. In this regard, it must be emphasized that Dextrotest is not intended to replace quantitative laboratory methods.

According to the data presented here, the results of the Dextrotest, with readings above 100 mg. %, appear to correspond somewhat better with those obtained with the Folin-Wu blood sugar method than with the Somogyi-Nelson method. The inability of the Dextrotest to register hypoglycæmia constitutes a deficiency inherent in the method from the standpoint of a definitive biochemical diagnosis. The use of whole blood offers an advantage as compared with a procedure that requires the preliminary separation of plasma or serum.[5]

SUMMARY

1. The results obtained with a rapid, bedside method for the estimation of the blood sugar (Dextrotest) are compared with those derived from standard laboratory analyses.

2. Subject to certain limitations, the procedure may be useful in emergency situations where urgent knowledge of the blood sugar content is desirable.

3. Gross hyperglycæmia can be recognized but the method is incapable of detecting hypoglycæmia directly.

4. The procedure is impracticable as a guide for the therapeutic control of diabetic patients.

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QUALITY AND QUANTITY IN MEDICINE

This is not only the age of anxiety; it is also the age of insurance. Never before in our western civilization have the insurance companies done so much business, and never before has there been so much preoccupation with protection against the hazards of life. With the growth of health insurance in various forms, interest in the quality and quantity of medical care given to insured persons must also inevitably grow. An index of this interest was provided at the annual meeting of the Canadian Public Health Association in Toronto when the Medical Care Section met on Monday, May 27, and heard speakers on the quality control of medical care and cost control in medical care.

Dr. Ogden Woodruff, consultant in medical practice to the Health Insurance Plan of Greater New York, opened the ball with a long and detailed description of the methods used by that plan to ensure that the one thousand participating physicians, working in 32 medical groups, and serving half a million people, would render a high standard of medical care. After listening to the formidable list of requirements for entry to the closed panel of physicians, one had the impression that New York must be an earthly medical paradise guarded by a H.I.P. angel with a flaming sword. Not only must the family doctor wishing to enter the plan be a graduate of an approved medical school, an intern of an approved hospital and a holder of a staff appointment in a voluntary or municipal hospital, but there is talk of adding an approved medical residency of two years to the list. The applicant for inclusion on the panel is interviewed at his office by an internist and later by a small committee to evaluate his attitudes towards patients and group practice. He may even have to write an examination of a multiple-answer type before his name comes before the Medical Control Board for final acceptance or rejection. What happens to the doctor whose application is rejected? Presumably the poor fellow must content himself with private practice among the millions of New Yorkers who are not covered by H.I.P. In other words, as Dr. Vincent Matthews of the Department of Public Health of Saskatchewan pointed out in discussing this paper, exclusion from a closed panel may do nothing to raise the physician's standards but simply segregate him from his fellows.

Dr. Matthews had some shrewd comments to make on this aspect of quality control. He noted that control in H.I.P. was exercised by the insurance agency (though admittedly through a board of physicians). He considered that it would be better if control was exercised by the doctors themselves. He also made a valid point when he indicated that in Canada we place more confidence on the examination of physicians by provincial licensing authorities and by the Medical Council of Canada than in private systems of recognition of fitness to practise. It would indeed seem a reflection on the licensing boards if their statement that a man is qualified to practise as a family physician is set at nought by other bodies. Furthermore, as Dr. Matthews pointed out, if every insurance agency is to set its own standards, the utmost confusion will result. The role of the insurance carrier should be one of co-operation with the medical profession in ensuring standards, and plans should indicate to the profession where these standards need tightening up. Control of medical care by the profession itself is not an unattainable ideal. This was shown by Dr. Matthews's description of the work of the very active assessment committee in the Swift Current area, elected by the medical profession of the area with broad powers granted by the district medical society.

Dr. Woodruff wisely introduced the definition of the word "quality" in his address. He rightly discarded the suggestion that quality of medical care means availability of medical care, and concentrated on the two possibilities that it might mean professional competence or that it might mean a patient-doctor relationship such that the patient was satisfied with the care he

was getting. It is clear that ideally these points of view should be incorporated in the definition, but Dr. Woodruff takes the view that "irrespective of its importance, a satisfactory doctor-patient attitude could not be accepted as a substitute for professional competence".

The physician's relationship to his colleagues is also considered an important factor in the success of an insurance plan, for Dr. Woodruff stipulates that the insurance company should have the right to terminate any contract with the physician if "a physician's personality is such as to make him constantly a thorn in the side of his medical confreres with whom he associates". In other words, "conform or get out". Some may find this thought a little disturbing. We could think of a number of thorns, whose value to the medical profession lies in the fact that they are thorns. One wonders indeed whether the rose of medical freedom can flourish without a few thorns.

With the realization that many of these remarks can only apply to partial coverage of an urban population, Dr. Woodruff introduced the further question of quality control in a plan with universal compulsory coverage. He said: "In establishing a mechanism for bringing medical care to all of its citizens through compulsory premium payments, it seems to me to be at least debatable whether government has not the added responsibility of seeing that its involuntary enrollees get medical care of satisfactory quality." This is a problem which bristles with difficulties, and it is clear that the difficulties can only be met in a situation where government has available large sums of money and large numbers of personnel. Unless a community is grossly over-supplied with doctors, practically all of those available will have to be used in the plan. In that case, policing the profession can only be done by the profession itself. Some of Dr. Woodruff's aids to quality control in these circumstances—encouragement of joint sharing of offices with colleagues, and extension of hospital privileges under supervision with compulsory staff conference attendance—have long been sought by the unfortunate general practitioners of Britain, but have been persistently ignored by their governments. Dr. Woodruff's paper, which will no doubt appear later in the *Canadian Journal of Public Health*, deserves close study, for it has many points which cannot be dealt with in a brief editorial. Perhaps the whole situation is best summed up in the remark of a later contributor to the session, when he said that the medical profession must "either give leadership or like what it gets".

Editorial Comments

THE "REBOUND" PHENOMENON IN RHEUMATIC FEVER

Steroids, salicylates and antibiotics all have a use in the treatment of acute rheumatic fever. The antibiotics diminish the recurrence of acute attacks of the disease by reducing the incidence of streptococcal infections.[1] The salicylates and steroids are employed on empirical grounds. Some have claimed that these drugs do no more than suppress symptoms.[2] Others have held an anti-inflammatory basis for their usefulness.[3] These substances, however, neither singly nor in combination can cure the disease. This then poses a problem as to how long treatment of an acute attack with these agents should continue. The question is impossible to answer in point of the exact number of days, as the natural history of an acute episode can extend from 20 to 113 days with an average duration of 84 days.[4] Cessation of treatment before the natural termination of the acute phase allows the disease to again assert itself and so produce the phenomenon of "rebound". This "rebound" may involve only the laboratory evidence of rheumatic activity (increased sedimentation rate, increased C-reactive protein, increased serum mucoprotein, etc.) or both the laboratory and clinical evidence of activity.[5]

Insufficient length of treatment would on the surface appear to adequately explain the "rebound". A closer look, however, casts doubt on this simple explanation.

The regularity and frequency of the "rebounds" after cessation of these drugs is far greater than one would expect from the natural polycyclic and undulating course of the disease.[3] The "rebounds" seem to bear no relation in time of their appearance to the length of time it takes the individual to rid himself of these drugs,[6] and the severity of the "rebound" is often more violent than the original illness.[7] If these drugs are anti-inflammatory, it is hard to explain the fewer "rebounds" one sees after salicylates than after steroids.[6]

To invoke other causes of "rebound", adrenal suppression after steroid therapy has been postulated but not substantiated.[8, 9] This would not account for occurrence of "rebound" after salicylate use.

Holt[10] has attempted to analyze the "rebound" in a study of 110 attacks of acute rheumatic

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fever. These cases were treated by steroids, ACTH, salicylates in low and high dosage, and combinations of salicylates and steroids. Some of the cases were managed under the Rheumatic Fever Study carried on jointly by the Medical Research Council and the American Council on Rheumatic Fever. The remainder of the cases were treated until the clinical signs had disappeared and the sedimentation rate was normal for three consecutive weeks or for a maximum of three months.

"Rebound" phenomena occurred equally in the steroid (30.6%) and in the salicylate (33%) groups. There was, however, a significantly higher incidence of "rebound" after high salicylate dosage (40.7%) than after low salicylate dosage (6.2%).

In analyzing the conditions associated with "rebound" (shown by laboratory in 20 instances, and by laboratory and clinical signs in 14 instances), Holt has found dental sepsis, β-hæmolytic streptococcal throat infections, lengthy illness preceding therapy, and early adolescence in females.

The importance of the "rebound" in relation to late sequelæ of the disease has not been established. Houser[11] and Holt[10] give no indication that permanent harm can result from it. However, if one accepts the view of Fischel[3] that the drugs used actually reduce inflammatory phenomena in addition to suppressing symptoms, then the "rebound" carries with it the same implication as the acute attack and should be vigorously treated. Just as there is disagreement about the treatment of an acute attack of rheumatic fever, the management of the "rebound" is also split into salicylate and steroid camps.

Holt has presented an interesting report, but one would be loath to accept dental sepsis as a major reason for increased sedimentation rate, fever, etc., unless one knew how severe this sepsis is. Such sepsis in young children has in the reviewer's experience produced little systemic reaction and rarely a rise in the sedimentation rate.

To return now to the prophylaxis of rheumatic fever by the use of intramuscular benzathine penicillin: Haas[12] has reported rises in temperature and increases in C-reactive protein and sedimentation rate following its use. One must keep this in mind lest these be interpreted as "rebounds" or relapses.

The incidence of "rebound" would seem to be different when the serum mucoprotein level is used as evidence of activity and an indicator to cease therapy.[13] A study similar to that of Holt but using this criterion would seem to be well worth while.

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CONSTIPATION

Every practitioner is aware of the plight of his constipated patients. The middle-aged female who cannot have a spontaneous bowel movement usually gives a history of several years during which she has used more vigorous laxatives in ever-increasing dosages, thus contributing to the quarter of a billion dollar a year sales of laxatives, as recently recorded in the United States.[1] This form of habituation or tolerance obviously serves no useful purpose. Factors responsible for this state of things include faulty dietary habits such as low-residue diets, deficient in non-absorbable cellulose bulk, together with low water-intake. (The average woman hardly drinks at all.) The well-known over-solicitous mother may start the patient on the wrong trend even in childhood. These faulty bowel-habits are aggravated by the rapid pace of urban living, where the pressure of work, social commitments or play leaves little time for defæcation. The medical profession shares the blame to a certain extent when some of its members advise their patients that one regular bowel-movement every 24 hours is essential for maintaining health.

Although chronic constipation is mainly a nuisance which calls for an elaborate ritual a few times a week over the months and years, it may nevertheless become a surgical problem, particularly in the elderly patient when fæcal impaction leads to colonic occlusion and all its consequences. Constipation must not be brushed off lightly, as it may well supply one of the early clues in the diagnosis of colonic or rectal malignancy. Alternating constipation and diarrhœa, together with the feeling of incomplete emptying after a movement, must always be viewed with some concern. Although the statement that digital rectal examination should be an essential part of any complete physical examination is now a truism, one still sees all too frequently instances where this advice has been disregarded with deplorable consequences. Certain internists with particular gastroenterological leanings go even so far as to suggest that sigmoidoscopy should be included in the routine physical examination of every patient. The importance of a stool examination for the presence of occult blood need not be re-emphasized.

Radiology is no longer the only means of diagnosing colonic malignancies, since exfoliative cytology is now being used for the demonstration of malignant cells in the proximal colon. This highly specialized technique is apparently giving very hopeful results in this particular field of application.[2]

Chronic constipation may not necessarily be the reflection of a depressed gastrocolic reflex; it may also be one of the manifestations of certain systemic diseases such as thyroid dysfunction, pernicious anæmia, or lead poisoning. In these cases, however, it is unusual to have constipation as the only presenting symptom; the latter is most of the time overshadowed by others more distressing to the patient. This somewhat neglected aspect of medical practice belongs to a field where popular health education could achieve excellent results in the line of prevention. Let us give it the importance it deserves.

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WOUND SHOCK

Although the treatment of wound shock is more vitally important in wartime than it is now, the possibility of a major disaster is always pending; succinct and up-to-date information on the matter should be welcome. This is provided in the latest Medical Research Council memorandum[1] published recently by a working party under the chairmanship of Sir Ernest Rock-Carling. This working party has almost completely rewritten the old war memorandum No. 1 on the same topic. In the lucid style and clear presentation characteristic of these opuscules, the assessment of the patient and his treatment are followed by appendices on various aspects of transfusions.

Even though most practising physicians are conversant with the principles involved in the treatment of the patient in shock, certain points bear reiterating. It is interesting to read that "the apathy described as being so characteristic of patients suffering from wound-shock in the First World War was probably due in large part to the free use of morphine". A warning is issued against the subcutaneous administration of this drug in a condition of shock, for little absorption takes place until the circulation is re-established and then all the subsequent doses which have been administered after the first apparently ineffective one are mobilized and may sometimes reach a toxic level. If vasoconstriction is not too severe to prevent the intravenous administration of the drug, this is by far the best route; otherwise deep intramuscular injections are recommended. Tourniquets, the time-honoured standby of first-aid practice, can be advantageously replaced by pressure-bandages if the latter are available. "If a tourniquet has already been applied, it is generally advisable to remove it, unless it can be seen that a main vessel is severed or a limb so severely mangled that it is unlikely to be saved and the tourniquet is found in a satisfactory position close by the site of injury."

In shock due to depressed circulation, resulting from abdominal or peripheral injury, the use of oxygen has little to offer. However, in chest wounds, particularly those due to blast, and also in pulmonary lesions resulting from irritants to the respiratory tract or poisoning by the inhalation of noxious gases, its use has a very definite place in treatment.

The topic of blood replacement in shock is now commonplace. In spite of the rule which says: *if in doubt, transfuse,* there are certain contraindications to transfusion. These include central nervous system injuries, which may cause vasodilatation without any severe loss of blood, thoracic injuries where the pulmonary tissue has been altered with consequent shift in the pulmonary circulation, or similarly when the lung parenchyma has been irritated by war gases such as phosgene, mustard or lewisite, and pulmonary œdema is the result.

Practitioners who may be called upon at a moment's notice to deal with such severe traumatic lesions as are encountered in car accidents, industrial disasters, blasts and fires, would do well to peruse this booklet, where all the important information is gathered and presented in an orderly and concise manner.

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A PHARMACEUTICAL PHILANTHROPIST

Henry Solomon Wellcome, one of the great philanthropists who have made a niche in medical history, was a most unusual man. He began life as an American citizen in Wisconsin in 1853, went into pharmacy, conquered the English market with his new "Tabloid" drugs, and ended up as a British citizen knighted for his services to medical research. His story is told in the recently published First Report of the Wellcome Trust, 1937-1956, in which the activities of this autocrat of the pharmaceutical world are described, and an account is given of the stewardship of his legacy to medical research. Sir Henry was a pioneer in the establishment of research projects by pharmaceutical houses, now become a commonplace. His life story should be read as an indication of the heights to which one man's enterprise and brains can carry him.

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Medical News in brief

EARLY BREAST CANCER

After discussing figures for results of treatment of breast cancer, Gray of Melbourne, Australia (*M. J. Australia*, 1: 410, 1957) makes various suggestions for the management of "early" breast cancer. He suggests that the initial investigation should include both breasts and the axillary and supraclavicular glands on both sides, abdominal and vaginal examinations, and x-ray examinations of lungs, skull, spine and pelvis. Biopsy excision of supraclavicular glands and of the gland-bearing tissue around the internal mammary vessels should be carried out, supplemented usually by biopsy of the primary tumour. If metastases are present in one or both of these glandular groups, simple mastectomy followed by irradiation is considered the best procedure. If both biopsies are negative, a radical operation without irradiation is probably best, except that if metastases are demonstrated in axillary glands removed, postoperative irradiation may be added.

CURLING'S ULCER

The odd phenomenon of gastro-intestinal (usually duodenal) ulceration after burns, known as Curling's ulcer, occurred in 20 out of 1000 patients treated at an army hospital in the U.S.A. for burns over a period of just over six years. Seven out of the 20 patients who had this ulcer had no signs or symptoms of it, but the lesion was found at autopsy. In nine cases the duodenum alone was involved, while in three cases the duodenum and the stomach had an ulcer. Three patients had a stomach ulcer alone, and one an ulcer in the duodenum and the jejunum. In spite of the low incidence, it should be noted that Curling's ulcer was common in patients with more severe burns. Studies of uropepsin excretion were made, but neither the level of uropepsin excretion nor the gastric acidity was of diagnostic value in predicting development of Curling's ulcer, although levels of uropepsin and gastric acid were high in severe burns. Curling's ulcer was not diagnosed until patients had developed an acute gastro-intestinal hæmorrhage or had a marked epigastric pain. The authors of the study, Hummel *et al.*, (*J. A. M. A.*, 164: 141, 1957) recommended prophylactic treatment of all severely burned patients with aluminium hydroxide or a similar antacid. Conservative medical management of bleeding Curling's ulcer is advised unless operation is absolutely necessary to save life.

LONG-TERM RESULTS OF THERAPY OF RHEUMATOID ARTHRITIS

This *Journal* has previously noted the findings during the first and second years of therapy in the controlled trials of treatment of early cases of rheumatoid arthritis with either cortisone or aspirin, started in 1951 by a joint committee of the Medical Research Council and the Nuffield Foundation in the United Kingdom. Comparisons are now made after three to four years in the groups treated with aspirin and with cortisone respectively. Both groups showed considerable improvement by the end of the first year, and the outcome after three to four years appears to have been quite independent of whether the patient had received either aspirin or cortisone. Serious complications of therapy were encountered only in the series given cortisone, and seven of these were transferred to aspirin therapy. This suggested that, with the passage of time, both patients and physicians had in some cases come to prefer aspirin to cortisone. In general in one-quarter of the patients in the series the disease went into remission, in a similar proportion the disease remained very active, and in the remaining half the disease remained slightly active. Only one-quarter of the patients became seriously disabled. On the whole aspirin seemed more often likely to prove satisfactory for long-term management of these cases.—*Brit. M. J.*, 1: 847, 1957.

CO-OPERATIVE RESEARCH ON CEREBRAL VASCULAR DISEASE

The U.S. Public Health Service is organizing a study of cerebral vascular accidents. Ten medical research centres have already joined the program, and it is expected that 35-40 institutions will ultimately participate. Institute grants have been made for the program, which is expected to run for five or six years, and is to be directed particularly towards the value of therapeutic measures and the selection of patients for surgical intervention. Data collected will be collated and evaluated at the University of Iowa, Iowa City.

SARCOIDOSIS AND PREGNANCY

Mayock and his colleagues from Philadelphia studied the effect of 16 pregnancies on ten patients suffering from sarcoidosis (*J. A. M. A.*, 164: 158, 1957). They noted that in eight out of the ten cases there was a temporary improvement of the disease condition during pregnancy, while in the other two patients no change occurred. The fact that no evidence of progression of the disease during pregnancy was observed is considered by them to suggest that tuberculosis has no association with sarcoidosis. It is possible that sarcoidosis has a deleterious effect on pregnancy, for in this small series two abnormalities of pregnancy were encountered—a case of premature delivery and one of stillbirth—while three cases of fetal abnormality were also noted.

(Continued on advertising page 42)

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GENERAL PRACTICE

DIZZINESS

J. A. VIRTUE, M.D., F.R.C.S.[C.],
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PATIENTS often present themselves complaining of a symptom which they call "dizziness". The specific cause of the symptom is difficult to find, because the problem is usually complex.

In order to evaluate the symptom correctly it is always necessary to obtain *an exact description* from the patient *of what he actually feels.* On questioning, some patients describe a feeling of turning, whirling, weakness, swimming, lightheadedness, swaying, pressure on the head, unsteadiness, a fear of "passing out", mental confusion or a loss of alertness.

Therefore, it is apparent that what the patient at first calls dizziness may really be one of a number of complaints which are unrelated in their pathogenesis. On the one hand there is a feeling of faintness or weakness. On the other hand there is a sensation of turning or of movement of the individual or his surroundings.

PHYSIOLOGICAL AND CLINICAL CONSIDERATIONS

A. The sensation of impaired alertness, *weak spells, faintness or actual syncope*—comes on rapidly and is usually of brief duration. There is rarely reduction in vital function with unconsciousness and convulsive movements. These symptoms are brought on by general reduction in cerebral blood flow and altered cerebral metabolism. There is a reduction in the cerebral oxygen utilization.

Examples of conditions producing this would be aortic stenosis, pooling of blood in the extremities and postural hypotension, anæmia and vasovagal attacks.

Often with these conditions there are accompanying autonomic nervous system disturbances, with pallor, cold perspiration, sometimes nausea, sometimes a thin pulse and low blood pressure. Once the patient lies down there is improved blood flow to the brain and recovery. Except for a continued feeling of weakness in some cases, the patient feels normal once again.

B. The sensation of *turning* or an attack of *vertigo* is usually associated with a lesion of the vestibular apparatus or connections of the vestibular nuclei in the pons and medulla.

Examples of conditions producing this would be: an eighth nerve tumour, Ménière's disease, localized vascular change and labyrinthitis.

Although not understood in detail, the *intracranial connections of these vestibular nuclei* have elaborate central pathways. These include connections:

1. With the nuclei of the external eye muscles, through the medial longitudinal fascicle; thus nystagmus or jerky movement of the eyes is sometimes associated with dizziness.

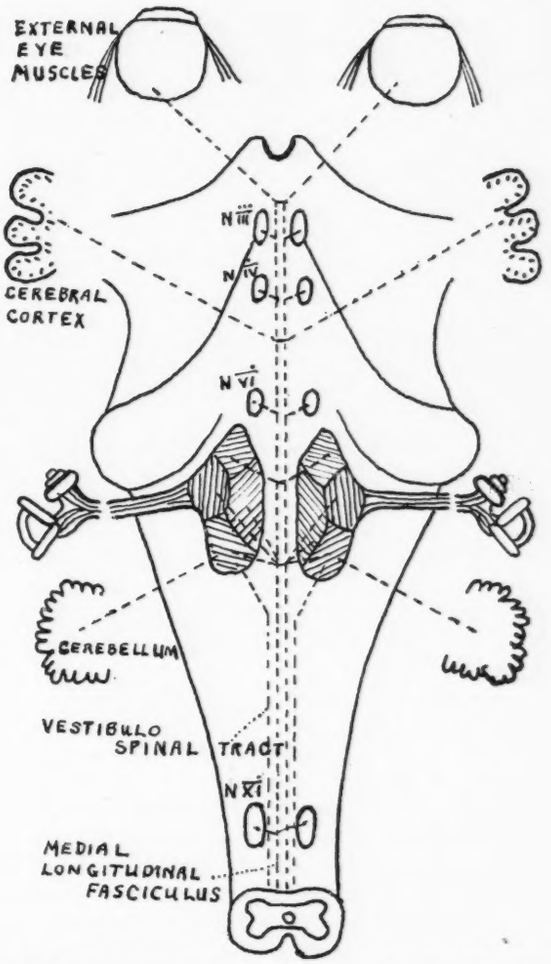

Fig. 1.—Scheme of the brain stem showing the intracranial connections of the vestibular nuclei.

2. With the cerebellum through branches of the vestibular nerve and the vestibulo-cerebellar fasciculus; so that muscular corrections in response to dizzy sensations are helped by the influence of the cerebellum on synergy and proper co-ordination of voluntary muscles.

3. With the motor nuclei of the spinal cord through the vestibulo-spinal tract. By this means a "reflex tone" is maintained by body musculature, especially the anti-gravity or extensor muscles, which are concerned with maintaining proper posture. The descending fibres of the medial longitudinal fasciculus conduct impulses to the neck muscles, affecting the posture of the head. Thus, in the presence of dizziness or altered body position, there is a tendency for compensatory body and head movements to be made in order to restore the body to proper orientation with the force of gravity.

4. With the cerebrum, making dizziness a conscious symptom. There is some indication that the sensation of dizziness has its representation in the temporal lobe near the auditory area.

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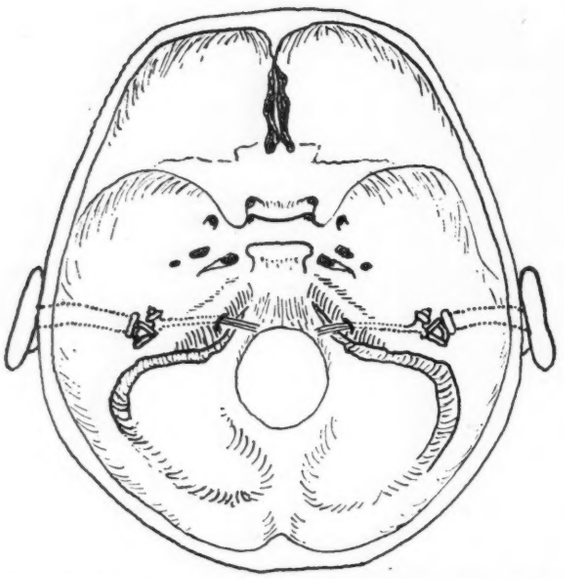

Fig. 2.—Diagram of the base of the skull internally, indicating the close relationship of the vestibule (balance organ) and cochlea (hearing organ) of the inner ear.

5. With the parasympathetic centres. The vestibular nuclei lie near the vagal centre and activity here is manifested by pallor, fall in blood pressure, nausea and vomiting—which sometimes occur when the vestibular apparatus is stimulated or irritated.

C. Localized *vascular change*, sometimes vascular spasm with resulting ischæmia of varying degrees, is often the cause of the complaint. The labyrinthine artery is an end artery and its branches are the sole supply to the cochlea or hearing organ and the vestibule or balance organ of the inner ear. It arises from the internal auditory artery which is a branch of the basilar artery. (Occasionally the internal auditory artery arises from the inferior cerebellar artery.)

In considering all the various intracranial connections of the vestibular nuclei, it is evident that any disturbance in circulation to the brain may cause a complaint of dizziness.

THE INVESTIGATION

The *history* pertaining to the complaint of dizziness should include:

(a) A description of the actual sensation which the patient experiences. Is it a feeling of *episodic weakness*? Is there a loss of vigour? Do the limbs feel weak? Is alertness impaired? Does the weak feeling progress to faintness or actual unconsciousness? Is the onset rather abrupt and is there complete recovery within a few minutes?

(b) A description of the *"turning" sensation* if that is present. Is it a momentary flash or prolonged for hours? Does it come on in complete rest while lying quietly or sitting in a chair, or is it associated with head and body movements, when the patient is moving about or getting out of bed in the morning? Is there a prodromal period of warning symptoms or is it a paroxysm without warning? Is it associated with physical or emotional fatigue? Does the patient ever actually fall down? Does the patient feel that he is turning or falling, or does he feel that the objects in his line of vision are moving?

(c) Any evidence of *ear disease*. Is there deafness, tinnitus, distortion of sound, or a feeling of pressure in the ear? Has the patient undergone a mastoid operation? Is the ear discharging or painful?

(d) Any symptoms suggesting disease of the *central nervous system*. Is there muscle weakness, double vision, numbness of the face, loss of consciousness or "blacking out"? Does the patient experience headache?

(e) Other miscellaneous and relevant inquiry. Is there excessive use of tobacco or alcohol or any drugs? Are there gastro-intestinal upsets, any previous injuries or operations, a history suggestive of allergy, or any chronic systemic disease? Is there a focus of infection in the teeth or respiratory system? Is the patient "high-strung"? Does the dizziness have any relationship to domestic or occupational strain?

THE EXAMINATION

A general physical examination should be carried out and diagnostic aid may be derived from urinalysis, blood examination, and serological and blood chemistry tests. However, the main examination is directed to the cardiovascular system and the nervous system.

A. General examination of the *cardiovascular system* should include a check on the colour of the face and lips and the type of breathing, percussion and auscultation of the chest and heart, examination of character, rate and rhythm of the pulse, blood pressure, and visualization of the retina and vessels seen on fundi examination. In some cases repeat examination after physical exertion, fluoroscopy of the chest, radiography of the chest, and electrocardiography may be carried out.

B. General examination of the *nervous system* should include a check on the cranial nerves, motor system, reflexes and sensory system. If any abnormality is found or suspected, an effort is made to determine the location and nature of the lesion. If a lesion of the brain is suggested, skull radiography, pneumoencephalography, angiography and electroencephalography may be used. Fluid removed by lumbar puncture may be examined; this is of particular aid in nervous-system injuries, infection, cerebrovascular accidents, and where a neoplasm is suspected. The spinal canal may be examined by introducing radio-opaque substances. Examination of the fundi and optic discs and visual fields is indicated in many patients.

C. In some cases, however, there is tinnitus, deafness or symptoms suggestive of ear disease. Here, a *complete ear, nose and throat* examina-

tion should be carried out, including examination of function of the inner ear by audiometric and vestibular tests. X-ray studies may be made to show the mastoids, internal auditory meati and any shift of the pineal gland. Hearing tests are carried out, since the balance and hearing organs are so closely related; this includes audiometric tests to distinguish between conductive and nerve type of hearing loss and a recruitment test to help rule out an eighth nerve tumour. Diplacusis, or difference of pitch between the two ears, is noted.

TESTS FOR BALANCE ORGAN FUNCTION

A *vestibular or caloric test* is carried out. It is best done in the office by stimulating the balance organ with cold air against the drum. Each side is tested separately by means of air blown through a Dundas Grant coiled speculum for 20 seconds, the air being cooled by ethyl chloride placed on the outside of the speculum. This may show a hypoactive or inactive or hyperactive balance organ on one side, or it may reproduce the exact sensation of the spontaneous dizzy attacks, thus helping point to the source of the trouble.

A *fistula test* should be carried out where there is a drum perforation and disease of the middle ear and mastoid is suspected or has been present for a long time. Here moderate alternating pressure is produced in the ear canal by the use of a Siegle speculum. Where increased air pressure produces dizziness and nystagmus, it indicates a breakdown of bone over the vestibular organ; normally the bony wall over the balance organ would protect it from this stimulation. However, this fistula test would be negative, even though there might be imminent danger of disease invading the region of the balance organ in the temporal bone, in cases where the vestibular organ was not functioning and where the caloric test outlined previously proved that the organ was inactive.

A check for *positional nystagmus* (a to-and-fro jerky movement of the eyes) is made. It should be understood, though, that in many cases of dizziness it is not possible to produce nystagmus by positioning the patient. The test is carried out in the following way. The patent, in the sitting position, is asked to look straight ahead with the eyes open. Then the head is held back and tilted to the left, then to the right, then bent forward, with the head down between the knees, and finally back again looking straight up at the ceiling. Each position is held for 10 seconds with the examiner watching for nystagmus. If nystagmus is produced, the position is held for 30 seconds and after a minute the position is renewed.

When nystagmus comes on slowly, is not easily repeated and is of brief duration, it is probably associated with a lesion of the vestibular end organ. The dizziness produced is quite severe. When the nystagmus comes on quickly after the head position is taken, is easily repeated and is not fatigable, it is probably associated with an intracranial lesion involving the central pathways of the vestibular system.

DIFFERENTIAL DIAGNOSIS AND TREATMENT

As the management of dizziness depends upon an accurate diagnosis, an effort should be made to search for the cause of the "dizzy" sensation.

1. *Medical Management Problems*

One of this group is *cardiovascular disease.* The most frequent findings are *hypertension* and *arteriosclerosis,* which may affect the labyrinthine artery itself or branches of the vertebral and basilar arteries, causing a feeling of slight dizziness or extensive brain stem syndromes. If the vascular lesion is situated where it causes disorder to the vestibular nuclei or their intracranial connections, the sensation is usually one of turning or vertigo-like.

One of the complaints associated with a "little stroke" may be that of dizziness. Here, a small thrombotic injury to the brain causes a sudden feeling of turning or of unsteadiness and may be accompanied by some degree of mental confusion, prostration and change of character of the individual. It is usually one of a series of episodes occurring in the older individual and sometimes happens during the night, when the blood pressure is at its lowest and the tendency to thrombosis at its greatest.

Another group of conditions is made up of lesions causing *episodic weakness, faintness* and rarely syncope with temporary suspension of consciousness. It is due to *reduced cerebral blood flow* and associated reduction in cerebral oxygen utilization.

Postural hypotension affects people with an *instability of vasomotor reflexes.* It occurs on sudden arising from a recumbent position or standing still in some otherwise normal people. Also, it is found following prolonged illness, where old age or nervous system disease causes weak, flabby muscles, and occasionally following sympathectomy which abolishes vasopressor reflexes.

Vasovagal attacks, associated with vasodilatation and drop in blood pressure, cause the ordinary faint. The attack occurs in the erect position and is relieved by lying down. Usually it is associated with great emotional excitement, during pain or following injury.

In *certain cardiac conditions,* such as Stokes-Adams syndrome, where there is a permanently slow pulse, in aortic stenosis, paroxysmal tachycardia, coronary artery disease, bradycardia, hypersensitive carotid sinus, and heart block, these symptoms may occur.

Other causes are laryngeal vertigo associated with a severe paroxysm of coughing, hyperventilation syndrome, hypoglycæmia, the menopausal syndrome, blood loss associated with acute in-

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ternal hæmorrhage, such as that due to peptic ulcer, and hysterical fainting associated with chronic psychiatric illness.

Petit mal epilepsy must be kept in mind; also lightheadedness associated with gastro-intestinal upsets, notably gall-bladder attacks and gastro-enteritis. In the occasional case, excessive *fatigue* seems to be the only possible explanation for the complaint of dizzy spells.

These *vascular and systemic causes* of dizziness are medical problems. The patient usually interprets his symptoms as being due to serious disease and so becomes extremely worried and anxious. Fortunately, the majority of conditions which produce recurrent weakness and syncope are not serious. Once the serious, less frequent causes listed above have been excluded, the patient can be reassured that his symptoms are due to a rather benign disorder. Where hypertension or arteriosclerosis is judged to be the cause, proper therapy should be instituted for the disease, and a program of physical limitations and a healthy mental outlook should be outlined to the patient.

2. *Impairment of Peripheral Structures*

Chronic middle ear or mastoid disease which causes dizziness should receive prompt attention. Toxic labyrinthitis may occur with administration of salicylates, quinine or streptomycin; or as a result of infections and diseases with high fever, especially "flu".

An acute vestibular failure may occur without an apparent focus of infection. This is the probable cause of the "epidemic labyrinthitis" which is seen. The condition is easily recognized by the sudden severe dizziness with vomiting which demands absolute bed rest. The symptoms slowly subside and after about three weeks the patient is usually well except for slight residual dizziness on sudden movement of the head; a few patients are left with a nerve type of hearing loss on the affected side.

Occlusion of the end artery to the labyrinth and labyrinthine hæmorrhage are dramatic and fortunately not common. Here there is deafness and often tinnitus as well as sudden dizziness. The course is gradual improvement of symptoms, usually with some unilateral hearing loss. The course is not influenced greatly by medication.

3. *Ménière's Disease*

Ménière's disease, or hydrops of the labyrinth, is a definite entity with deafness, tinnitus, attacks of dizziness, distortion of sound and occasionally a feeling of pressure in the ear.

On examination the ear canal, drum and middle ear are normal in appearance. The attacks of dizziness recur and vary in different patients from violent, whirling vertigo to a sensation of unsteadiness. Between attacks there may be less severe dizziness associated with head movements. During an attack there is no loss of consciousness and no paralysis, and when it is over there is good memory for the events during the attack. After a sound sleep, perhaps aided by sedation, the patient once again feels healthy.

The diagnosis depends on *audiometric findings*, including positive recruitment, diplacusis and a type of deafness where there is loss of clarity as well as diminution in the loudness of sound.

Temporal bone sections indicate that Ménière's disease is associated with an increased intralabyrinthine pressure and fluid imbalance. Therefore, treatment is directed towards alleviating autonomic imbalance and vasomotor change affecting the blood supply to the inner ear or labyrinth.

General management: Where a diagnosis of Ménière's disease is made, the nature of the illness, with its varying periods of remission, should be explained to the patient. He is told that medication must be tried which has helped diminish the symptoms for others. The treatment must be carried out for an indefinite period as required to relieve symptoms, and he must train himself to carry on a more regular and less strenuous type of existence.

The *acute attack* must be treated early if treatment is to be effective. Scopolamine hydrobromide, 1/150 grain sublingually, has a sedative and anticholinergic action and helps the severe attack. It may be repeated in 20 minutes if necessary, but care must be taken in using it on individuals over 50 years of age, who may become euphoric or have an exaggerated reaction. Atropine, 1/100 grain intramuscularly, or dimenhydrinate (Dramamine or Gravol), 100 mg. as a rectal suppository or 50 mg. intramuscularly, may be used.

To relieve arteriolar spasm, nicotinic acid given in doses sufficient to get a slight flush is used, approximately 50 to 100 mg. being given 20 minutes before meals. Histamine given subcutaneously and sublingually has a vasodilator and perhaps a histamine-desensitization effect.

Long-acting labyrinthine depressants and antihistamines, such as 25 mg. of meclizine (Bonamine), given daily before breakfast are helpful.

To combat excess interstitial fluid the patient is put on a low sodium intake. This includes no added salt and the avoidance of salty foods. This may be helped by giving KCl, 10 to 20 grains t.i.d., which has a mild diuretic effect and may influence conductivity of nerve impulses. The drug is given for three-day intervals, alternating with three-day rest periods.

Drugs combining antispasmodic and sedative effects are helpful in some cases, such as Donnatal, given three or four times a day.

Where indicated by the history, an elimination diet should be used to find any offending allergen, as a specific food allergy exists in a very few cases. If the patient smokes, a period of tobacco omission for four weeks should be tried and continued if helpful.

In intractable dizziness, where all medical treatment has been exhausted, surgical treatment may be considered. Labyrinthine ablation through an endaural mastoid opening is sometimes done when one ear is affected and the hearing in the other ear is fairly good. In the cases where the hearing on the affected side is good, partial eighth nerve section may be carried out by an intracranial operation in an attempt to spare the hearing in this ear.

4. *Motion Sickness*

This is a constitutional disorder, usually dating back to childhood. It varies greatly among individuals and is probably due to the up-and-down motion stimulating the utricle of the vestibular organ. The semicircular canals are also probably stimulated. It is treated by lying down and the administration of a vestibular depressant such as dimenhydrinate (Dramamine).

5. *Benign Postural Dizziness*

Here the cause is less clear. It is a benign affair, probably due to brief change in cerebral blood flow affecting the vestibular end organ or its central vestibular pathways. Or it may be associated with a mildly abnormal labyrinth requiring just that little "push" of quick change of position to set it off. At any rate, anxiety and the insecurity of recurrent weak sensations or of recurrent partial failures of the labyrinth may lead to limitation of activity and fear of attacks. The patient requires much encouragement and reassurance; definite vascular and central nervous system disease must be ruled out. The patient is given an explanation of his trouble and instructed to avoid "quick" changes of position. Attention is focused on improving the general health.

6. *Anxiety Tension State*

Often, dizziness is an expression of increased nervous tension. Here, questioning usually brings out a story of a sense of imbalance or queerness, or a sense of insecurity. The patient often has a fear of dying or of "passing out". Then the story tumbles out and the description of the dizziness becomes more vague as symptoms of gas, palpitation, chest pain, insomnia, etc., are related.

If no organic disease is found in the inner ear or elsewhere, this patient should be told that tension gives rise to feelings of uncertainty and insecurity and that these feelings may appear to him as dizziness. Usually a thorough examination is required here to point up to the patient the innocuousness of his trouble and the absence of any serious underlying disease. This knowledge will aid in the relief of some of his apprehension; but the cause underlying his anxiety must also be searched for and treated. Phenobarbital ¼ to ½ grain t.i.d. or some similar sedative may be helpful. It is often best to tell the patient that the drug is to help decrease his tension and will thereby allay the sensations of dizziness.

7. *Central Nervous System Disease*

Here the first consideration is eighth nerve tumour in which the signs and symptoms depend on the expanding cerebellopontine angle tumour disturbing the eighth and other nearby cranial nerves. Treatment is surgical.

Multiple sclerosis, once diagnosed, receives palliative treatment.

Cerebral contusion, with its varying degrees of œdema and multiple small hæmorrhages, presents a fairly clear picture. The treatment is merely the treatment of the brain injury, the end result depending on the severity of the injury.

But *post-traumatic dizziness* is a bigger problem. After even mild concussions dizziness may continue, especially with changing body and head positions. A basal skull fracture involving the temporal bone may be found or suspected by the findings following the injury. Here persistent dizziness suggests vestibular damage, probably resulting from vascular change to the labyrinth or residual defect due to the original injury. In other cases the decision is difficult concerning the organic or functional state or the compensation neurosis present; when a decision is made, one often wonders whether it is right. Time is the important factor, and settling compensation is essential.

SUMMARY

Diagnosis of the exact cause of dizziness is difficult. Therefore, treatment must be directed in many cases simply to allaying symptoms present.

Commonly, when a patient comes in with "dizziness", the actual sensation is one of weakness, loss of alertness or lightheadedness. It is usually associated with cardiovascular or systemic disease and due to changed cerebral metabolism and reduced blood flow to the brain. However, a patient may describe his complaint as a definite "turning sensation" of himself or his surroundings. Here, there is usually some disorder, often vascular, affecting the vestibular apparatus of the inner ear or the connections of the vestibular nuclei.

Because (a) periods of spontaneous remission often occur; (b) several drugs are often used at the same time; and (c) psychic factors play a prominent part in the sensation of dizziness, evaluation of drugs used is exceedingly difficult.

A patient should not be labelled as a case of Ménière's disease unless the history and audiometric findings indicate this diagnosis. If all the criteria for diagnosing Ménière's disease are not present, the symptoms should be treated but the patient should be rechecked at intervals for other signs or progressing vascular or nervous system disease.

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The symptom of dizziness is often worsened by fear. In some cases the fear of the presence of a brain tumour must be dispelled by thorough examination and adequate management. In other cases the patient has a fear that in a certain situation the dizziness will recur; here the patient requires much encouragement, and the course of medication must be re-evaluated from time to time.

In most cases of dizziness, following a careful examination, it is usually possible by one means or another to prevent or subdue the attacks.

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THE GENERAL PRACTITIONER AND TUBERCULOSIS*

J. Z. GILLIES, B.A., M.D., *Toronto*

MASS X-RAY SURVEY of the general public, preemployment radiography and other methods of detecting tuberculosis have become so numerous in Canada that the question arises: Has the family physician any problem left in tuberculosis after all these case-finding and preventive measures have come into almost universal use? This question is answered, in part at least, by experience with tuberculosis in my practice in the last two years. During that time I have had four cases which seem to indicate the trend in recent years, and I shall give a brief history of these cases.

The first case was that of an elderly man of 81, whom I had seen occasionally for several years, suffering from chronic bronchitis and acute asthmatic attacks. A radiograph of his chest in 1952 was negative for any active disease. In August 1955, because of abdominal distress and retention of urine, he was sent into Western Hospital and eventually operated on for appendicitis. He was followed up at the chest clinic, found to have tuberculosis, and sent to sanatorium in December 1955; he died the following March.

The second case was that of a woman of 79, very active mentally and socially, who developed several attacks of acute cystitis over the course of a couple of years. These occurred several times while she was in Florida but always cleared promptly with sulfathiazole. In the spring of 1955 she developed another acute attack which cleared promptly except that the urine continued to show pus despite sulfonamides and antibiotics. Intravenous pyelography showed dilatation of the renal calices on the right side and marked obstruction of the ureter near the bladder. Cystoscopy confirmed the presence of obstruction, and it was impossible to pass a fine ureteral catheter. Tubercle bacilli were identified in the urine, and at operation the right kidney and ureter were removed. Pathological report confirmed the diagnosis of tuberculosis of kidney and ureter. Radiographs of chest were negative for tuberculosis. She had a stormy convalescence but after nearly a year of treatment with streptomycin and isoniazid she made a complete recovery. She has since had an operation for gall-stones.

The third case was that of a Chinese of 59 years who reported with chronic cough and loss of weight. Radiograph and sputum were both positive for tuberculosis and he is now in sanatorium.

The fourth case was that of a man of 71 who had led an active life until two years previously, when he felt run down and lost considerable weight. Radiograph and sputum were positive and he went into sanatorium, where he had intensive treatment for a year with good results. He signed himself out against the advice of the staff, and is at home at present. Successive sputum tests have been negative, but he is still a likely case for recurrence of the disease.

There is one common factor in these cases, which I wish to emphasize. It is the advanced age of these patients: 60-80 years. In three out of four, the history indicates a flare-up of an old healed lesion under stress or acute infection.

It indicates that there is still a dangerous source of infection among this older group in our community and we must be constantly on the alert for signs of flare-ups in the 60's to 80's. We must not be lulled into a false sense of security by the x-ray report: pulmonary tuberculosis, inactive at present. Any acute infection may light up that old tuberculous lesion and change the whole picture. This is the type of case where a more liberal use of the sputum bottle is invaluable. Whenever these cases have an acute respiratory infection, a sputum test should certainly be done, for that is the time when they most often have a positive sputum.

Koch's dictum, "Jedermann hat am Ende ein bisschen Tuberculose," is no longer true, but that age group where it was true must still be watched carefully until, by the relentless laws of life expectancy, it has disappeared from this stage we call life.

This is the problem in one extreme of life; what about the other extreme? It would be impossible to overemphasize the importance of tuberculin testing in the young as a case-finding mechanism. Trimble, in an editorial in *Diseases of the Chest*, June 1956, points out graphically the advantage of starting chemotherapy at the earliest possible moment after infection has been proven. By the time infection has been proven by x-ray, the disease has already progressed a long way and treatment is more difficult. If chemotherapy were started shortly after a case

*Presented at the Annual Meeting of the Medical Advisory Section, Ontario Tuberculosis Association, November 1, 1956.

changed from tuberculin-negative to tuberculin-positive, it would be of tremendous value to the patient.

Trimble quotes figures to show the low percentage of tuberculin-positive cases in the present generation up to 18 years; it is as low as 10% in many localities. Here is another opportunity for the family doctor to play a major role in the control of tuberculosis. By testing this rising generation as he sees them in his office he will have a record of their reaction, and later on, if the child is exposed to infection or becomes debilitated for unexplained reasons, comparison of a further tuberculin test with the original one gives the key for early treatment even before the x-ray picture can supply the answer regarding infection.

The family doctor sees disease in its earliest phases, and his recognition of the first signs of acute infections such as pneumonia and administration of appropriate treatment in the initial stages abort the infection and get the patient back to health and wage-earning promptly. Here is another opportunity for early diagnosis where the economics of illness are tremendously serious.

I would like to see every general practitioner in Canada become tuberculosis-minded, and do a tuberculin test on every child and young adult who comes to his office. With earlier recognition and earlier treatment we may still be able to obliterate tuberculosis in our generation.

1435 Lansdowne Ave.

Men and Books

THE OSLER LIBRARY, MONTREAL

AT THE 27TH annual meeting of the Curators of the Osler Library on April 15, 1957, the chairman, Dr. Lloyd Stevenson, announced that a most gratifying donation had been made to the Library.

This was the direct result of an effort initiated by Dr. Wilder Penfield, one of the library curators. Dr. Penfield at last year's meeting had suggested that a determined effort be made to obtain endowment funds for the Library. Its sources of revenue were not large, and were quite inadequate to buy books for the strengthening of the Library. A committee was therefore appointed to explore the matter.

The curators were now delighted to learn that the Wellcome Trust of London had come forward with a most generous offer. This, in brief, was a gift of £5000 outright, together with further grants of £1200 annually for the next 25 years. The sole condition attaching to this munificence was one dictated by the requirements of international finance, namely, that the money so donated was to be spent only in the sterling area. Still, most of the bookbuying (for this historical collection) would in any case be on the other side of the Atlantic, and, in addition, such things as special repairs and bindings could be carried out in the United Kingdom under the terms of the gift.

The books bought by means of this money would of course become part of the Osler Library, but it has been arranged that they will be housed in a special room in the University, to be known as the Wellcome Camera. Dr. Francis explained that the word "camera" is the Latin word for a room, and avoids conflict with the title of the present Wellcome Library in London. It has also been used in the case of a special section of the Bodleian Library, the Radcliffe Camera.

If proof were needed, this gift is striking evidence of faith in the vigorous life of the Osler Library. Only the unfortunate lack of funds has so far prevented the expansion of its work and influence beyond its already varied activities amongst students and all those interested in medical history. The annual report of the Library this year shows increasing use of its facilities, and refers in particular to the far-flung lecturing activities of Dr. Lloyd Stevenson as Professor of the History of Medicine.

The gift from the Wellcome Trust has been a great encouragement, but the fact remains that it cannot be applied to expenditures in North America. The Library still needs dollars, and whilst acknowledging the constant and invaluable help of its many friends it looks for the support of all those who would like to be associated with its unique influence.

The curators received with great pleasure at this meeting a fine addition to the Library's collection of incunabula. This came from Dr. W. M. Fitzhugh, Jr., of Monterey, California. It was formally presented, as from the curators, in honour of Dr. Francis, the librarian. It is an exceptionally fine copy of a mediæval work on therapeutics entitled *Aggregator, sive de medicinis simplicibus*. The author was Jacobus Dondus, and it was published about 1470 by the "R" printer, so-called from his employing a special form of capital R in his printing, and because his name was unknown till a century or more ago. The book is rare; it is said that there are only five other copies in North America. It is in perfect condition with wooden covers and leather and metal clasps, and is a delight to the eye with its rich rubrication in red, blue and green. Dr. Francis acknowledged the gift with deep appreciation of Dr. Fitzhugh's continued and discriminating support of the Library. H.E.M.

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MEDICAL MEETINGS

ANNUAL MEETING OF THE QUEBEC DIVISION, C.M.A.

The 19th annual meeting of the Quebec Division of the C.M.A. was held May 2, 3, and 4, 1957, at Ste. Adèle-en-Haut, Que., a resort in the Laurentians about 40 miles north of Montreal. To say that it was unusually successful is not to disparage other meetings of the Division, but rather to emphasize its growing strength. There was a registration of nearly 200 doctors and 71 ladies, a figure higher than at any previous meeting; and the general sense was that of great satisfaction with the proceedings.

Perhaps it was the clear (but cool!) spring weather; perhaps the charming setting of the meeting place; perhaps the well-chosen and interesting program; perhaps the novelty of holding the meetings in one large hall round which the commercial exhibits were grouped, thus saving time in visiting them between events. Whatever it was, everyone was sorry to see it end.

The program displayed a well-balanced mixture of medicine, surgery and the specialties. This representation was especially well maintained in a symposium on the palliative control of cancer, in which different aspects were dealt with by experienced men. Its closing paper by Dr. Norman Delarue was aptly entitled "The Philosophy of the Treatment of Cancer of the Breast". The exactly right philosophic approach was achieved in the discussion and presentation of the factors involved. Dr. Delarue would have had us believe that the previous speakers had anticipated him in anything he could say on the subject, and then proceeded to show how a well-stored mind can set already familiar material in a refreshingly new light.

At the business meeting of the second afternoon Dr. James Quintin handed over the Presidency to Dr. Georges Leclerc, the president-elect being Dr. F. W. Fitzgerald. The question of forming a Grievance Committee to supplement the work of the Committee on Ethics was dealt with at length, but was finally left for further consideration by the Executive. Dr. A. D. Kelly, General Secretary of the C.M.A., gave a clear and concise summary of the content of the famous Bill 320 regarding hospitalization, but little discussion was possible so far as Quebec Province was concerned since no information is yet available on the stand the provincial government will take in the matter.

On Saturday morning a lively discussion on chronic inflammatory disease of the colon was followed by excellent papers by Drs. Paul Fiset and V. Pavilanis on virus disease. It was pointed out that it is now possible to accurately diagnose the various forms of commoner virus disease if the technique outlined is followed. The closing papers on cerebral hæmorrhage and on Parkinson's disease brought out some extremely stimulating discussion. Dr. Claude Bertrand of Montreal in particular described the work he had been doing in alleviating some of the terribly disabling effects of this disease; indeed one case was shown to the meeting in which practically complete restoration had been achieved. Dr. R. T. Johnson of Manchester spoke of the great difficulty in selecting cases of cerebral hæmorrhage for operation. Dr. Harold Elliott showed a motion picture of the various phases of Parkinsonism.

Dr. Renaud Lemieux, President of the C.M.A., instals Dr. Georges Leclerc of Montreal as President of the Division. Centre: Dr. F. W. Fitzgerald, Lachute, President-elect.

The Friday evening banquet was marked by the presentation to Dr. Walter Scriver of a piece of Wedgwood china on the occasion of his much to be regretted retirement from his long and devoted service as chairman of the Executive of the Division. Dr. Scriver will be succeeded by Dr. Renaud Lemieux, the President of the Association.

The guest speaker at the banquet was Dr. Eugene Forsey, of Ottawa, Director of Research, Canadian Labor Congress. Dr. Forsey, speaking on labour and national health, said that the million-odd members of the Canadian Labor Congress, together with their families, represent approximately three or four million Canadians. The views of the Labor Congress on national health were expressed in a bulletin issued in the summer of 1956. A similar document is shortly to be issued containing the views of the Quebec section of the Catholic

The outgoing president, Dr. T. J. Quintin of Sherbrooke, makes a presentation to Dr. Jessie Scriver of Montreal, while Dr. W. de M. Scriver (standing, left) looks on.

Syndicates on the same topic. The philosophy of this organization regarding health issues is based on the assumption of human equality, namely that "we are all equal in the eye of the law and the sight of God." The lecturer quoted a seventeenth-century leveller, who had stated: "poorest he who liveth in England hath a life to live as the richest he." Everybody is entitled to the same medical care in Canada, and Canadians at the present time are not getting equal quality or quantity of health care. Those who fare worst in this matter are the income group in the brackets between $1500 and $3000 a year. These apparently spend an average of $88 to $125 a year for medical care. There is also a great discrepancy in the money spent on medical matters between the large families ($15 a year), and the small families ($45 a year). A similar discrepancy exists between the rural and the urban populations. Seventy-five per cent of all physicians are to be found in towns of 10,000 population and over, and 90% of all specialists are to be encountered in the same conditions. This also applies to dentists. The solution of the medical profession to extend the already existing facilities in order to include everybody does not satisfy members of the Labor Congress. At present, these do not cover all the population; they merely cover about 50%—and at that, only 35% receive medical and surgical benefits. According to Dr. Forsey, even if the same plans were extended at the same rate as they have been in the last 10 years, it would take a very, very long time for them to cover the whole of the population. The plans so far have cultivated the most fertile fields of the population. Those who have been left out are made up mostly of bad risks and, as such, either could not or would not be accepted at the present rates. The lecturer did not think that the present plans were worth being supplemented by public subsidies since they are inadequate, cover only part of the payment and do not guarantee availability of service. Moreover, they would involve a large private bureaucracy with considerable duplication in the work, as several plans are at present in effect. Labour's aim is to obtain a nation-wide scheme administered by the Provinces and providing a nation-wide minimum of service. The Dominion Treasury would have to pay the bulk of the cost as several provinces have too poor tax-resources to be able to finance such a scheme. Although this means socialism, the lecturer maintained that medical traditional free enterprise had failed in its attempt to reach this goal. This scheme should come into effect in stages, it should be clearly defined beforehand and each stage should follow each other within a reasonably short period of time. The recently adopted hospitalization insurance plan was described as "the first timid halting step" which should have been taken a long time ago. The following objections to the plan were mentioned and brushed off rather lightly. The plan need not be too centralized, it would not imply too large a bureaucracy, the physicians would not necessarily become public servants, nor would the plan be run by lay people or "medical ignoramuses" (also described as numskulls). Medical obscurantism should be counterbalanced by outside influence, coming preferably from scientific fields other than medicine. There was no place for anarcho-syndicalism or such attitudes as "the health-scheme service for the doctors" as the mines for the miners and the railways for the railway workers. The last and probably the most formidable objection, namely the cost, was answered by the fact that apparently nobody knows this figure and no firm estimate can be obtained. The lecturer, however, pointed out that Canadians have been spending 6½% of the national income on alcohol and tobacco, and that the cost of health at the present time is about 5%. That there was reason to improve medical care in Canada can be derived from the fact that in 1956 there were 17 million labour days lost through illness, which, as the lecturer pointed out, is 13 times as many as the number of days lost through labour strikes. Although he described himself as not being addicted to State-action as such, Dr. Forsey said that the cost of medical care has reached such an extent that mutual help is necessary. "Bear ye one another's burden" should stand as the motto behind Labour's approach to the health problem.

The Quebec Division was particularly happy to be host to the following distinguished medical visitors who contributed their share in the scientific program: Dr. N. C. Delarue and Dr. D. R. Wilson of Toronto; Dr. A. Parker Haydon of the Massachusetts General Hospital, Boston; Dr. R. T. Johnson of Manchester, and Dr. E. M. Robertson of Kingston.

Dr. A. D. Kelly, General Secretary of the C.M.A., Dr. J. C. C. Dawson, President of the Ontario Medical Association, Dr. Glenn Sawyer, Secretary of the O.M.A., and Mr. B. E. Fremo, Assistant Secretary of the O.M.A., made valuable contributions to the discussions held during the business meeting.

CANADIAN PUBLIC HEALTH ASSOCIATION

The Canadian Public Health Association held its 45th annual meeting in conjunction with the 8th meeting of the Ontario Public Health Association at the King Edward Hotel, Toronto, May 27-29, 1957. As usual, there was a very full program of plenary and sectional meetings. On Tuesday evening the President of the Canadian Public Health Association, Dr. L. A. Pequegnat, and the President of the Ontario Public Health Association, Dr. D. F. Damude, held a reception before the annual dinner. At this dinner, honorary life memberships in the Canadian Public Health Association were presented to Miss Florence Emory of Toronto and Professor E. G. D. Murray of London, Ontario, and also *in absentia* to Professor Fraser Brockington of Manchester, England, and Dr. F. W. Jackson of Ottawa. The dinner speaker was Dr. G. E. Hall, President and Vice-Chancellor of the University of Western Ontario. At the dinner the President-elect, Dr. Stewart Murray of Vancouver, was introduced to the company.

For the practising physician, the meetings of the Medical Care Section of the C.P.H.A. were probably the most interesting. In the opening session, Mr. John Hornal of Toronto stressed the current shortages in professional staff in public general hospitals. There is a particularly severe shortage of nursing personnel, which is likely to become somewhat worse in the near future. Directors of nursing and operating room nurses are particularly scarce. Dietitians, physical and occupational therapists, pharmacists, and certified laboratory technologists are all also in short supply, but the greatest percentage shortage exists in the field of medical-social workers. Dr. John S. Crawford of Toronto gave a very timely discussion of problems of rehabilitation in a general hospital, based on his own work at the Toronto Western Hospital.

The first subject to be dealt with in the Monday afternoon session was "Quality Control of Medical Care" in which Dr. Ogden Woodruff of the Health Insurance Plan of Greater New York described the methods used in H.I.P. to ensure quality of professional service. The two principal mechanisms for maintaining standards in the medical groups employed are the contract between the Board of Directors and each medical group which detailed the benefits to be provided and the legal requirements of partnerships of physicians. The second is a medical control board which sets standards for work of the medical groups and for qualifications of physicians accepted for membership. Standards have been set for medical records, preventive services for adults, prenatal care and well-baby care during the first year. Pædiatricians give children's services up to at least the age of three and are available for consultation on patients up to the age of 12. All groups must have at least one scienti-

fic conference monthly, apart from business meetings, and all specialty services must be given from the group centre. Employment of office assistants is strongly encouraged. Attempts have recently been made to combine research with practice by offering young physicians the opportunity to practise half-time and employ the rest of their time in research at a medical school or hospital. A health education service is maintained. External medical audits have revealed certain fields in which medical care falls below the standard desired. Certain categories of disease, such as anæmia, hypertension, peptic ulcer, diabetes, and in children rheumatic fever, congenital and rheumatic heart disease, nephritis and urinary tract infections, show weakness in management. Dr. Woodruff defined quality as not being particularly linked with the comfort and satisfaction of the patient, but rather with medical competence. He was concerned to note that insurers against hospital costs had shown little or no sense of responsibility in the matter of the kind of institution in which their members were hospitalized.

Dr. Vincent Matthews of the Department of Health of Saskatchewan discussed Dr. Woodruff's paper and noted that H.I.P. control was done by the insurance agency, involving the use of a closed panel. He believed that it would be better if control were exercised by the doctors themselves. He stressed, as Dr. Woodruff himself had admitted, that the standards to which H.I.P. adhered were practicable only in a large urban area. He felt that in Canada more confidence was placed on the examination of physicians by provincial licensing bodies and by the Medical Council of Canada. Exclusion by an insurance agency might not raise a practitioner's standards but simply separate him off from some of his colleagues. He thought a probationary period in a plan was valuable, and was afraid that if every insurance agency set its own standards, confusion would result. It is important for all insurance plans to co-operate with the medical profession in ensuring standards; plans should indicate to the profession where standards needed tightening up.

There had been few audits of medical care in Canada, and those had only usually been undertaken to solve a particular problem. Dr. Matthews thought that, with the extension of health insurance in Canada, it might be expected that payments would be limited to hospitals giving good standards of care.

Dr. Harding leRiche, Toronto, discussed the control of costs in a prepaid medical care plan, noting that although between 1930 and 1953 in Canada, relative personal expenditures had increased substantially for alcohol, tobacco and transportation, expenditures on personal and medical care had not relatively increased. Between 1946 and 1953 the income of physicians in private practice had remained at a constant 1% of the total assessed income of all taxpayers in Canada. Other graphs were shown to illustrate the fact that between 1951 and 1955 the average income of the physician in Canada had increased at about the same rate as the weekly wage of an industrial worker. As regards Physicians' Services Incorporated, utilization rates per thousand participants had increased over the period 1949-1956 from 2350 to 3890, with corresponding increase in payment. Increase in costs was due to increase in services, increase in schedules, and increase in proportion of expensive services, mainly surgical. The speaker suggested that it was unlikely that real medical need had increased since 1947, but the more prosperous and leisured the society becomes, the more it worries about its health. As long as insurance plans were voluntary, this situation was reasonable, but if universal compulsory service appeared, there was a real danger that the medical profession would have excessive demands made on them without an increase in income. He felt that, in any prepaid medical care plan, the participant in a group ought to have a financial stake in his premium. Lastly he discussed the system of control of costs in P.S.I., stating that medically sponsored plans could do a certain amount to control costs, but that physicians and hospitals must do most of the rest.

This paper was discussed by Dr. J. Osler Lockhart of Hamilton, Ontario, from the standpoint of a general practitioner. He said that the test of any health protection plan was the degree to which it met medical needs and the quality of care given. There was a steady, slow movement in Canada from indemnity plan to service plans. There would always be variations in cost of medical care from patient to patient and from physician to physician. He drew attention to the need for analysis of physicians' expenses in providing medical care; this figure was increasing all the time and should be taken into account.

On May 28, the Medical Care Section considered planning for hospital bed requirements. The session was introduced by Dr. Malcolm G. Taylor, Consultant to the Ontario Hospital Services Commission, and the two chief participants were Dr. V. M. Hoge, Assistant Surgeon General, U.S. Public Health Service, and Mr. John Osborne, Department of National Health and Welfare, Ottawa. Dr. Hoge outlined the Federal Hospital programs in the United States, and commented on the number of beds sufficient to serve a population; this figure must depend on the purpose of the modern hospital. In his opinion, the hospital should be the health centre for a community. He made the point that hospital need was not the same as hospital demand (i.e. what persons were able and ready to buy). In general in the U.S.A. the demand is less than the need. Mr. Osborne did not feel able to set any ratio of beds to population on theoretical grounds, but preferred the pragmatic approach. In Canada figures quoted for active treatment beds had varied between 4.6 and 7.5 and for chronic beds between 1.5 and 2 per thousand population. The present figure in Canada seemed short of the ideal. Immigration, which particularly affected Ontario and Quebec, was an important factor in creating bed shortage, particularly because many immigrants come from areas of Europe where hospital beds are much utilized. He noted the amazing variations between bed capacity and utilization across Canada. It was therefore impossible to say when starting a hospital plan for a province that the figure required would be the same as in another province with the same type of plan. Hospital planning must include planning for domiciliary care, otherwise cases would have to be unnecessarily retained in hospital. In the past not enough attention has been given to convalescent and chronic accommodation, but the climate may be changing. In discussion, Dr. Hoge mentioned that the concept of function of a chronic diseases hospital had changed; it used to be a place for old crocks; now it served for long-term care of patients of all ages with a fair prognosis and a need for rehabilitation. Two domiciliary care programs had been started in Canada, and the city of Toronto was actively considering a third one.

Dr. Gordon Hatcher of Hagerstown, Maryland, commented on changing patterns of medical care and insurance plans. He said that the principal change in medical care in recent years had been the introduction of a third party, the insurer, though there had in the past always been some third party, such as the licensing body or the legislator, to come between the patient and the doctor. Among the changing factors affecting medical care he listed changing epidemiology, new techniques in diagnosis and therapy, growing specialization with organization of physicians into groups and an increase in referrals, intervention of the state and planning, and the transfer to taxation and premiums of costs previously met by the individual or by philanthropists. Two questions which required an answer were—How is the cost of drugs affecting the cost of medical care?—How are the plans affecting the relative incomes of the general practitioner and the specialist? It used to be assumed that the fee-for-service method of payment could not work, but this had been adequately disproved. There is probably room for a small deterrent fee for physicians' services, but it is questionable whether this is any use in the case of drugs or hospital services.

On Wednesday, May 29, the Section of Medical Care went into the question of chronic diseases. The first

paper was read by Dr. F. B. Roth, Deputy Minister of Public Health, Saskatchewan, on chronic diseases in Canada. He said that chronic disease used to be the Cinderella of medicine, but it appeared now to be ready to go to the ball. In the past much difficulty had been encountered in attempting to define a chronic disease; we should stop trying to define it and realize that acute and chronic disease were not really separate entities. Many chronic diseases are not curable, but there is always something we can do until the case file is closed by death. It is wrong to separate medical and social aspects of such diseases, and the problem is to integrate treatment with other aspects and not have isolated programs. The rehabilitation should start much earlier and should begin in acute disease institutions, if it is to be more than a salvaging operation. Any program of chronic disease must go beyond the medical needs and provide for the social, economic and spiritual needs of the patient as well. Dr. K. C. Charron of the Department of National Health and Welfare, Ottawa, read a paper on chronic diseases in the Canadian Hospital Program. He began by listing the various levels of service for chronic diseases provided, e.g. the general hospital, special hospital, convalescent hospital, nursing home, rehabilitation centre, the doctor's office and the home. It was essential to ensure that a case was being cared for at the right level; this implied assessing the needs of the individual and reassessing them from time to time. He felt that in Canada a compromise should be adopted between the two philosophies of providing separate institutions for chronic disease or caring for these patients in a wing of a general hospital. The effective utilization of hospital beds for long-term care is a very difficult problem, because of the pressure on physicians to use these facilities where they are not really needed. The needs of the patient, though paramount, must be related to the needs of others, and there must be a free flow of patients between various levels of care. Any admission policy must retain a close physician-patient relationship. Admissions could be classed as those with favourable rehabilitation prognosis, poorer rehabilitation prognosis, likely alleviation by hospital care, and terminal cases. Though screening committees might be used for admissions, there must be close consultation with the family physician. Admission should imply active treatment and there should be a practical discharge and readmission policy. Dr. Charron dealt with the staffing of chronic disease facilities, and pointed out that the social service was unfortunately in the weakest part of the program, though there were shortages of all classes of trained personnel, because this was not a popular field of work. In discussion, Professor E. G. D. Murray of London, Ontario, wisely remarked that chronic diseases were chronic because of our total ignorance of their causation. This ignorance could only be overcome by work on human subjects, since chronic disease was impossible to produce in animals. Wholehearted research into the causation of chronic disease was the first priority. Dr. Roth summed up the discussion by saying that the patient with a chronic disease needs a manager who will manage his whole treatment program. This manager could be the family doctor, the public health physician or the social worker. He personally thought it should be the family doctor, but a true family doctor of a new type.

ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

The Royal College of Physicians and Surgeons of Canada announces that the 1957 Annual Meeting will be held at the Sheraton-Mt. Royal Hotel, Montreal, on Friday and Saturday, October 18 and 19, 1957.

Association Notes

WHERE DO I STAY IN EDINBURGH?

It is abundantly clear that a very large attendance of C.M.A. members and their wives may be expected at the Joint B.M.A.-C.M.A. Annual Meeting in Edinburgh, July 18 to 25, 1959. Already 650 men, women and children are on the list of our official travel agent, University Tours Ltd., 2 College Street, Toronto.

All members who contemplate the trip to Edinburgh are urged to make their intention known to University Tours regardless of whether they propose to use this agency or another to arrange their trip. The important reason for this step is that the files maintained by University Tours will provide the basic information on housing requirements which will permit the B.M.A. to make assignments to visiting Canadians.

Edinburgh is not abundantly supplied with de luxe hotels, and if your preference is for a corner suite overlooking the gardens you may be asked to settle for something less pretentious. Secondary hotels are more numerous and a large number of rooms are available in accommodation which is used for the influx of visitors to the annual Edinburgh International Festival. Private hospitality in the homes of Edinburgh doctors will be provided for the large number of Canadians who will wish to take advantage of this kind offer.

The British Medical Association must necessarily assume absolute control of all available bedrooms in Edinburgh for the period Saturday, July 18, to Saturday, July 25, 1959, and the task of housing a record number of overseas visitors will be materially assisted if C.M.A. members will refrain from attempts at private arrangements.

The assignment of accommodation will not be made until the extent of the demand is much clearer than it is at this date, but all C.M.A. members may be assured that their needs and, as far as possible, their desires will be met. To be certain that you are on the list for Edinburgh accommodation, do not fail to file with University Tours your intention of attending the meeting. An information form for your convenience will be found on page 1082 of this issue.

ARE YOU A SURGEON?

Even if you use a scalpel or suture only occasionally, you will want to know what is going on in Canadian surgery. From October 1 you will be able to inform yourself more easily of advances in the Canadian surgical scene, because on that date the first issue of the quarterly *Canadian Journal of Surgery*, published by the Canadian Medical Association, will appear. To ensure your receiving this journal from the very first number, you should subscribe now; there is a subscription form on page 776 of the issue of May 1.

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B.M.A. - C.M.A. Conjoint Annual Meeting
Edinburgh, July 18 - 25, 1959
INFORMATION FORM

NAME.....

ADDRESS.....

I shall be accompanied by.....

(If any children please state their sex and present age) .....

I prefer to travel by ship .....
by air ..... (a) regular schedule
..... (b) charter flight

I prefer to travel First Class .....
Tourist Class .....
Cabin Class .....

Ships from Canada have only two classes (First and Tourist). Ships from New York also carry Cabin Class.

I prefer to leave from Montreal .....
Quebec .....
New York .....

In addition to Edinburgh, I wish to visit the following:

England	Russia	Portugal	Germany
Holland	Hungary	Denmark	France
Switzerland	Ireland	Czechoslovakia	Norway
Spain	Belgium	Yugoslavia	Finland
Sweden	Italy	Scotland	Austria

I wish to travel on a conducted tour. Yes..... No .....

I prefer independent, arranged travel. Yes..... No .....

I wish to rent a self-drive car. Yes..... No .....

I wish to travel by chauffeur-driven car. Yes..... No .....

I wish to travel on motor coach tours. Yes..... No .....

I expect to be absent from Canada for ..... weeks.

I prefer to arrange my tour in advance of the Edinburgh meeting .....
after the Edinburgh meeting .....

I understand that accommodation in Edinburgh will be available, Saturday, July 18 to Saturday, July 25.
I am prepared to accept the housing assigned by the B.M.A. Committee. My preference is for:

Hotel..... Rooming house..... Private hospitality.....
(Please indicate in numerical order)

I wish to leave Canada in April .....
May .....
June .....
July .....

I wish to return to Canada in July .....
August .....
September.....
October .....

I wish the following class of land travel. De luxe .....
Standard .....
Thrift .....

On De luxe travel, rooms have private baths throughout—hotels are all de luxe and first-class.
On standard travel, rooms have private baths wherever available—hotels are all first-class.
On Thrift travel, small, comfortable, specially chosen hotels are used. Rooms do not generally have private baths.

My local travel agent is .....
.....

IT IS CLEARLY UNDERSTOOD THAT THE COMPLETION OF THIS FORM IN NO WAY BINDS ANY MEMBER OF THE CANADIAN MEDICAL ASSOCIATION

Please complete and return this form to:

UNIVERSITY TOURS LIMITED, 2 College Street, Toronto.

PUBLIC HEALTH

OTTAWA NEWSLETTER

(From the Department of National Health and Welfare)

APPETITE CONTROL AND OBESITY

The only logical cause for overweight is eating too much for the activity being carried out. The problem is to find and correct the causes for this imbalance between calories and energy expenditure.

Many current articles and reviews attest that even moderate overweight favours the development of degenerative diseases, and increases the mortality when such diseases occur. Weight control should be held out as a desirable goal to all adult men and women, since it is much easier to exercise some continuous control than to suddenly try to take off an excess. There is evidence that repeated and alternating gains and losses in weight may be especially bad for coronary arteries.

How does this excess weight accumulate? It is easy to say that overeating causes overweight, and there is abundant evidence that a person can lose weight if he eats little enough. But the subject is not as simple as this makes it appear, and every doctor should appreciate some of the background.

Racial influences may be present, but give at most only a predisposition to obesity, the ultimate result depending on actual caloric balance.

Endocrine obesity is now narrowed down to a small group, most of whom can achieve some control by adjusting the diet. The old idea of the pituitary gland as a prime factor has now been replaced by a hypothalamic explanation of Frohlich's syndrome. Similarly, the thyroid no longer explains everything. Indiscriminate use of thyroid preparations has often suppressed what little function there was, and led to real obesity. Adrenal and gonadal glands can be implicated in certain unusual distributions of fat. Cushing's syndrome (adrenal cortex) may give extra fat on the upper portion of the body, while gonads deposit it on the hips. In most cases an excess appetite, perhaps stimulated by emotional factors and operating through the hypothalamus, *plus* a decrease in activity, are responsible.

Since many obese persons, and others not yet obese but gaining weight, cannot or will not seek psychiatric help, it is necessary for the doctor to be aware of these emotional needs. Eating is a common method of combating anxiety, a gratification that may even begin in infancy.

Food may also be a symbol of friendship or even of love. Many hostesses who are insulted if guests fail to gorge, or wives who cater to their husbands' likes rather than good nutrition, may be literally killing them with kindness. In this they are aided by recipes and prepared mixes making it easier and easier to provide hundreds of calories in small volume. Some men are aware of the need to cut down on their food portions but they just cannot do it because it seems to lessen their feeling of being big or important. Eating may also symbolize hostility, self-punishment etc.

In all cases it is wise to study the emotional aspect carefully rather than attempt weight reduction at any cost. In fact 2 and 3 year follow-up studies show that very few people achieve lasting weight control without other adjustments in their lives and attitudes, and often the doctor has lost his patient because of too-rigorous diets.

Much of the present tendency to overweight may have arisen from the era when fat babies were considered healthy, and when the effort seemed to be to get everyone to grow bigger and faster. That effort was often the result of an attempt to overcome or avoid tuberculosis, which has now been influenced by other means. But people keep on eating heartily and forcing children to eat more than they need.

In present-day life our calorie needs are smaller because of shorter working hours, mechanization, the automobile and spectator sports. Even middle-aged people who appear to be as active as they were at thirty, tend to conserve energy by avoiding unnecessary movements and trips; and their basal metabolism has decreased a bit, too. But they keep on eating in much the same manner as they always have, thus heading straight for obesity. A conscious effort toward weight control is needed, and the doctor can help greatly with large doses of emotional support and analysis, guidance, or reassurance.

L. BRADLEY PETT, Ph.D., M.D.

LETTERS TO THE EDITOR

HIATUS HERNIA

To the Editor:

I was interested to read the article by Dr. H. S. Ford on "The Complications of Hiatus Hernia" in the *Journal* of April 15, 1957, p. 636. In particular I was interested in his comments on etiology.

During recent years hiatus herniation has become increasingly recognized as a pædiatric problem and I think Dr. Ford's assertion that the vast majority of hiatus hernias must be acquired needs further examination. There have been reports of large series of cases in infancy and childhood.[3, 9, 10] The subject has recently been reviewed in some detail from the pædiatric point of view.[8] In the year 1955, 53 cases of hiatus herniation were diagnosed in The Hospital for Sick Children, Toronto, of which 25 cases were diagnosed in the first month of life and 45 during the first year of life.

There has been no satisfactory long-term prospective study of the condition, so that the natural history is relatively unknown. My own experience and a study of the literature indicates that symptoms tend to occur most frequently at the extremes of life, though they may occur in between under special circumstances, for example during pregnancy. This is probably related to anatomical factors concerned with fixation of the œsophago-gastric junction below the diaphragm and the size of the diaphragmatic hiatus. These influence the competence of the œsophago-gastric mucosal valve which prevents reflux[2, 4-6, 8] and consequent digestion œsophagitis.

I therefore consider it possible that a considerable proportion of hernias are in fact primarily congenital, irrespective of the age at which the lesion is discovered. These hernias may produce symptoms during the first nine months or so of life and then improve, only to return in later life when anatomical changes occur with age favouring herniation, gastro-œsophageal incompetence and reflux. It may even be that during the clear interval of life the hernia reduces spontaneously only to recur with aging. Perusal of the literature and our own experience suggests that serious complications, leading to death if untreated, may occur in up to one-fifth of cases over the years.

Dr. Ford's paper brings to our notice the complications of the condition and therefore performs a timely service. I would like to add a plea for alertness to the possibility that the condition exists in early life.

PAUL R. SWYER, M.R.C.P.(Lond.)

Research Institute,
Hospital for Sick Children,
Toronto, May 8, 1957.

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ABSTRACTS *from current literature*

MEDICINE

Increased Erythropoiesis Induced by Androgenic-Hormone Therapy.

B. J. KENNEDY AND A. S. GILBERTSEN: *New England J. Med.*, 256: 719, 1957.

In this comprehensive review the authors discuss the erythropoietic effect of the prolonged administration of androgenic hormones. In approximately one-third of patients with metastatic disease, treated with androgens, an appreciable increase was noted in the red cell count and the hæmoglobin value, despite little or no effect upon the metastatic malignant process. In certain cases a marked polycythæmia occurs, which disappears on cessation of androgenic therapy.

This erythropoietic effect of the androgens has led to their use in the treatment of a variety of anæmias, sometimes with good result.

Of 68 patients with advanced breast cancer treated with androgens, 35% showed evidence of increased erythroid activity. The authors also present examples of various anæmias favourably influenced by treatment with testosterone. They advocate further investigation of the value of such treatment in the different forms of anæmia.

NORMAN S. SKINNER

Infections Complicating Cortisone Therapy.

F. P. SMITH AND E. A. CLEVE: *New England J. Med.*, 256: 104, 1957.

The basic mechanism of action of cortisone is still incompletely understood, but there is no evidence to indicate that it can cure disease through an influence upon the etiologic agent. Cortisone apparently modifies the response of the host to disease and, while this modification may be of advantage in certain situations, profound changes may be brought about in the immunological mechanisms, resulting in very serious consequences.

Six cases are reported in which serious infection developed as a complication of cortisone therapy. The complicating infection caused death in three of the six. The authors stress the danger of serious infection developing as a complication of corticosteroid therapy and the likelihood of its insidious progression because of its masking by the action of cortisone.

NORMAN S. SKINNER

Pulmonary Nocardiosis: Report of a Case Complicated by Tuberculosis.

E. R. HALL AND D. A. COOLEY: *Dis. Chest*, 31: 453, 1957.

Although much attention has been given recently to fungous infections of the lung, relatively few cases of pulmonary nocardiosis have been described and in most of them the disease was in the terminal stages. The apparent rarity of the disease is largely due to failure to recognize the clinical manifestations and findings of nocardiosis. Moreover, similarity between nocardiosis and pulmonary tuberculosis from a clinical and roentgenographic standpoint and the similar morphology of the causative organisms may lead to an erroneous diagnosis of tuberculosis in many cases of pulmonary nocardiosis. Even greater confusion may arise where the infections coexist. In this paper the writers describe a patient with pulmonary nocardiosis and tuberculosis in whom the latter infection was not recognized prior to lobectomy. Specific antituberculosis therapy was instituted 14 days after operation and a dangerous spread of the tuberculous process was controlled.

Nocardia asteroides is an ærobic, Gram-positive, acid-fast organism which grows readily on a variety of simple media, the colonies appearing wrinkled and granular. Culturally and morphologically the organism is closely related to *Mycobacterium tuberculosis*.

Nocardia asteroides produces a granulomatous lesion usually containing an exudate in which pink or black granules are demonstrated microscopically. In man nocardiosis is usually contracted by air-borne contamination but the organism may be introduced by trauma and small cutaneous puncture wounds.

Symptoms of nocardiosis are usually respiratory including chronic productive cough and occasional hæmoptysis. Malaise, chills, fever, anorexia, weight loss, and night sweats are common. Headache, nausea and vomiting may indicate cerebral involvement, a not infrequent complication.

In the patient described, diagnosis of pulmonary nocardiosis was firmly established before operation and the systemic manifestations of the disease were adequately controlled by sulfadiazine. Although tuberculosis was suspected from the time of initial examination, identification of the tubercle bacillus was not possible. After operation a dangerous spread of the tuberculous infection occurred while the fungus disease remained under control with sulfadiazine. A possible fatal outcome was averted by final recognition of fulminating pulmonary tuberculosis and institution of appropriate therapy. To the knowledge of the writers, no previous case of coexisting pulmonary nocardiosis and tuberculosis has been reported. The patient made a complete recovery under treatment of both diseases.

S. J. SHANE

SURGERY

The Therapeutic Effect of Hypothermia in Experimental Hæmorrhagic Shock.

A. H. POSTEL, C. REID AND J. W. HINTON: *Ann. Surg.*, 145: 311, 1957.

Experimental evidence is produced to show that dogs in apparently irreversible shock from hæmorrhage may be saved by hypothermia. Of control animals subjected to a three-hour hæmorrhage to a blood pressure of 40 mm. Hg followed by transfusion of all the blood lost, 20% survived for 24 hours and 13% for one month. Cooling to 27° C. (by rectum) after one hour of hæmorrhage enabled 93% to survive 24 hours and 80% for one month. This is considered a significant therapeutic effect, and a clinical trial of hypothermia for the treatment of certain shock states is suggested.

BURNS PLEWES

The Fallacy of the Conventional Radical Neck Dissection for Papillary Carcinoma of the Thyroid.

G. CRILE, JR.: *Ann. Surg.*, 145: 317, 1957.

The lymphatic drainage of most papillary carcinomas of the thyroid is to the paratracheal and mediastinal nodes, and the secondary lymphatic invasion is to nodes deep to the carotid artery as well as superficial to it. En bloc dissection of the primary lesion and its metastases is therefore impossible, and sacrifice of the sternomastoid muscle is indefensible. Many papillary carcinomas, like carcinoma of the prostate, are amenable to hormonal treatment. The thyroid stimulating hormone may be sup-

pressed by the administration of desiccated thyroid. A plea is made to avoid performance of mutilating block dissections for this disease. BURNS PLEWES

Surgical Complications of, and Splenectomy for, Collagen Diseases.

E. CARLSON AND J. P. HUDSON: *A.M.A. Arch. Surg.*, 74: 381, 1957.

Duff listed rheumatoid arthritis, rheumatic fever, systemic lupus erythematosus, periarteritis nodosa, dermatomyositis and scleroderma as collagen diseases. Four cases of lupus erythematosus are described in which gastrointestinal bleeding, abdominal pain, mesenteric thrombosis, pancreatitis and rupture of the colon occurred. Two of these had periarteritis nodosa. One of them appeared to have been arrested after a steadily progressive deterioration by splenectomy. Cases of lupus erythematosus with hypersplenism and purpura were also improved by splenectomy. Rheumatic fever cases were not helped by splenectomy, but in rheumatoid arthritis some encouraging results have been obtained. It is suggested that some cases resembling acute appendicitis but with a normal appendix may be cases of periarteritis nodosa or "necrotizing arteritis."

It may be that splenectomy is effective in collagen diseases as a form of shock therapy or perhaps by a hormonal effect. Its use is experimental thus far.

BURNS PLEWES

Giant Neurofibroma of Mesentery.

W. B. LEACH: *A.M.A. Arch. Surg.*, 74: 438, 1957.

A large tumour of the mesentery of the ileum was removed from a young man in the Vancouver General Hospital. It was a plexiform neurofibroma. He showed no other stigmata of von Recklinghausen's disease and there was no evidence of recurrence five years later. But after six years, café-au-lait spots and bluish intradermal lesions had appeared. BURNS PLEWES

OBSTETRICS AND GYNÆCOLOGY

Fetal Postmaturity and Sequelæ of Induction of Labour for Postmaturity.

F. J. BROWNE: *Brit. M. J.*, 1: 851, 1957.

A review of hospital reports shows that there are very large variations in the frequency of induction of labour for postmaturity without any significant differences in the perinatal mortality rates. In certain hospitals the induction rate is 30 times that of others in which induction for postmaturity is done.

In one hospital with 5000 deliveries in a year it was not done once, yet the stillbirth rate was the seventh lowest in 32 hospital reports, and the Cæsarean rate was 1.8%, the lowest in all the reports. There were no deaths from postmaturity before or during labour.

The complications occurring in 596 surgical inductions for postmaturity are reviewed. They include long induction-delivery intervals and a high Cæsarean rate (6.2%), the sections being usually done for prolonged labour due to disordered or abnormal uterine action.

It is suggested that many cases of so-called postmaturity are really examples of slow maturation of the fetus and placenta, and that as good or better perinatal mortality rates can be got in these cases without induction. Others may be due to the occurrence of conception in a very long menstrual cycle.

The higher fetal mortality in postmature babies as compared with those born at term can be adequately explained by the larger size of the infants and the longer duration of labour.

If, because of the larger size of the baby, there is disproportion, the case should be treated by trial of labour. Induction of labour is not the modern treatment for disproportion, at least in primigravidæ.

ROSS MITCHELL

Influence of Selective Induction of Labour on Mortality in Hæmolytic Disease of the Newborn.

O. D. FISHER: *Brit. M. J.*, 1: 615, 1857.

The results of 143 pregnancies in cases of Rhesus incompatibility delivered spontaneously or by selective premature induction of labour are reviewed. There is a notable lowering in the total mortality in the induced group (16%) compared with that of the group delivered spontaneously (29%). The severity of the disease was probably greater in the induced group, as twice as many exchange transfusions were performed and the average hæmoglobin level was lower than in the group spontaneously delivered. The beneficial results of selective premature induction of labour are also illustrated by the individual case histories.

The time of induction was based on the previous maternal history and on a clinical assessment of the individual patient. Selective premature induction of labour is thought to reduce the total mortality from hæmolytic disease of the newborn. ROSS MITCHELL

Shock in Obstetrics.

D. E. REID: *Am. J. Obst. & Gynec.*, 73: 697, 1957.

A review of maternal mortality indicates that a significant number of deaths continue to be due to shock. These deaths are largely preventable by more careful obstetric management in hospitals with the facilities to give emergency treatment of shock.

Except for myocardial infarction and the occasional case of sepsis, the treatment of shock as herein defined depends on early administration of blood in amounts adequate to restore the effective blood volume. Lack of adequate blood replacement, if it does not result in death, may lead to severe renal and pituitary damage. It is apparent that shock in obstetrics cannot be treated effectively by blood obtained from a blood repository outside the hospital or from donor lists. It can be met only by the hospital's own blood bank and by the storage of adequate amounts on the delivery floor. It is suggested that no hospital be allowed to care for pregnant women if it is unable to meet this essential requirement.

ROSS MITCHELL

THERAPEUTICS

Present Knowledge of Nystatin, An Antifungal Antibiotic.

R. BROWN AND E. L. HAZEN: *Tr. New York Acad. Sc.*, 19: 447, 1957.

Nystatin is a polyene antibiotic produced by *Streptomyces noursei*. *In vitro* it specifically inhibits the growth of a wide variety of pathogenic and saprophytic fungi, exhibiting both fungistatic and fungicidal properties. It has marked therapeutic action in mice experimentally infected with *Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Sporotrichum schenckii,* and *Candida albicans*. In oral moniliasis in rabbits its prophylactic and therapeutic effect is striking.

The investigation of nystatin in man has been concerned chiefly with moniliasis. However, the broad *in vitro* spectrum and the results in animals suggest that therapy in other fungus diseases might well prove satisfactory if the requisite mode of treatment were established. It has been ascertained that, in the treatment of disseminated coccidioidomycosis with nystatin, three cases were favourably influenced by intravenous administration, but that two cases with meningeal involvement were not influenced and terminated fatally. The nystatin did not pass from the blood into the spinal fluid. In man it is difficult to secure very significant blood levels, e.g. 0 to 3 μg./ml. of serum after a dose of 200,000 units given intramuscularly twice a day, but as high as 40 to 45 μg./ml. when 200,000 units are injected intravenously four times a day.

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Most favourable reports on the effectiveness of nystatin in various manifestations of moniliasis are now appearing. The increased incidénce and severity of these infections, particularly as sequelæ to therapy with broad-spectrum antibiotics, have demonstrated need for such an agent. As a rule, good to excellent results are obtained with almost no side effects.

The side effects elicited by nystatin depend upon the route of administration. Intravenous injections in cases of coccidioidomycosis caused sclerosing of the veins, and initial injections were accompanied by severe shaking, chills, fever and malaise. Intramuscular injections induced severe pain and tenderness at the site of injection. Administered topically or orally, however, it appears to be remarkably free of toxic reactions. No instances of allergic reactions or of contact dermatitis or urinary tract symptoms have been reported. The incidence of nausea, vomiting and diarrhœa has been low.

The low toxicity and high effectiveness of nystatin for prevention and therapy of moniliasis have led some observers to conclude that it should logically be administered prophylactically when the broad-spectrum antibiotics are required for debilitated patients, diabetics, infants (particularly premature infants), and pregnant women.

Nystatin is therefore a valuable and specific therapeutic agent for the various forms of moniliasis in man.

S. J. SHANE

DERMATOLOGY

Radiologic and Pathologic Bone Changes Associated With Urticaria Pigmentosa.

E. STARK, F. W. VAN BUSKIRK AND J. F. DALY: *A.M.A. Arch. Path.*, 62: 143, 1956.

The authors present a case of urticaria pigmentosa with marked bone changes. Clinically the lesions were typical of urticaria pigmentosa and a skin biopsy showed numerous mast cells in the upper corium. Radiologically, they found thickening and decrease in the number of trabeculæ with widened intertrabecular spaces of apparent decreased density, resulting in a net-like appearance. The lesions were symmetrical and were most striking in the humeri, femora, pelvis, lumbar vertebræ and ribs. In the ribs, the changes were similar to those seen in multiple myeloma or in metastatic malignant disease. Rib biopsy of a radiologically involved area showed the presence of numerous nodular lesions in the marrow spaces. A large proportion of the cells forming these nodules were mast cells. They suggest the term mast cell granuloma of bone for this condition.

ROBERT JACKSON

The Outcome of Patients with Herpes Zoster.

J. M. DE MORAGAS AND R. R. KIERLAND: *A.M.A. Arch. Dermat.*, 75: 193, 1957.

The authors review 916 cases with the diagnosis of herpes zoster or post-herpetic neuralgia. The duration of the post-herpetic neuralgia was used as the index of the severity of the process. With increasing age the number of cases and the severity of the post-herpetic neuralgia increased. There were only 24 cases under 20, but there were 270 in age group 60-69. Only 4% of those under 20 had pain for longer than one year, as compared with 37% of those between 60 and 69.

Trigeminal post-herpetic neuralgia consistently lasted longer in all age groups and the incidence of other serious complications was higher. Lymphoma was diagnosed in 39 cases.

Medical treatment included many divers substances (from aspirin and cobra venom to Protamide to vitamin B_{12}). Surgical treatment of post-herpetic neuralgia was only of very occasional benefit. The authors state that they found no specific measures that affected markedly the natural course of the disease.

ROBERT JACKSON

RADIOLOGY

The Abnormally Situated Azygos Vein.

R. N. ARMEN AND C. S. MORROW: *Circulation*, 14: 1079, 1956.

The aberrant azygos vein is easily recognizable on posteroanterior chest films, while the normally situated vein is difficult to identify.

A case is reported in which distension of an aberrant azygos vein was demonstrated radiologically during periods of right-sided heart failure, and in which the distension disappeared when the patient recovered from heart failure. Distension of the vein was demonstrated radiologically in the supine and Trendelenburg positions when the patient was free of heart failure. Distension was more marked in the Trendelenburg position. Early right-sided failure may be identified by the demonstration of distension of an aberrant azygos vein.

It is the opinion of the author that the aberrant azygos vein provides the clinician with an unusual sign that can focus attention upon increased venous pressure in the superior and inferior venæ cavæ and the portal vein.

S. J. SHANE

INDUSTRIAL MEDICINE

Optimum Time for Return to Work Following Various Major Cardiovascular Disabilities.

JOHN J. THORPE: *Indust. Med.*, 25: 329, 1956.

Evaluation of a person with cardiovascular disability for return to work is a highly individualized matter. The question of optimum duration of disability following various cardiovascular disorders is discussed. Information is derived from studies available in the literature, supplemented by that obtained during a brief survey of the records of 318 cases occurring in the Manufacturing Operations and the New York Office of the Esso Standard Oil Company during 1955. In this company, it is the policy of the Medical Department to use a generous sickness benefit program constructively to ensure optimum recovery from an illness before return to work. This, together with an active periodic examination program, gives a fairly complete picture of the history of the individual, his illness and the problem of returning him to work.

Consideration of the data permits the suggestion of certain arbitrary statements about average length of disability and certain criteria for measuring cardiovascular fitness. These include the following: (1) Coronary insufficiency will usually result in three to four weeks' absence. (2) Myocardial infarction will cause from 12 to 16 weeks' disability. (3) Congestive heart failure, irrespective of its etiology, usually means four to six weeks' absence. (4) Cerebral vascular disease produces between two and six months' absence. (5) Symptomatic essential hypertension without major cerebral, cardiac or renal involvement produces on the average from two to five weeks' disability. (6) Thrombophlebitis will result in three to four weeks' absence. (7) Varicose veins treated medically will average about a week of absence. Where surgery is undertaken four weeks will usually be lost from work. (8) Severe peripheral arteriosclerosis is not a common cause for absence. Where it is, the absence will be measured in months, and return to full duty is unlikely.

The author draws attention to the variation of individual cases in the groups. He points out also that the figures outlined are average. In his opinion, except in the obvious case, the only sure way to judge the individual's capability is a carefully observed trial at work. This should be tried in every case where failure will not endanger the employee's life or the safety of his fellows.

MARGARET H. WILTON

OBITUARIES

MAJOR EARLE HOWARD ANDERSON, D.S.O., died recently in Germany, at the age of 44. He was born in Digby, N.S., in 1913 and received his early education at the Digby Academy. After his graduation from Digby Academy, he entered Acadia University, Wolfville, where he received his B.Sc. He was a graduate of McGill University Medical School where he had taken a keen interest in neurology and diabetes.

A large part of his young life had been spent in the Armed Forces. From 1940 to 1945 he served as Medical Officer of the Seaforth and Black Watch Regiments, and Field Ambulance Units. While serving in Italy he was awarded the D.S.O. After his discharge from the Army he took up civilian medical practice in Digby. In 1950 he re-enlisted in the Medical Corps and saw service in Korea as Commanding Officer of the Twenty-fifth Field Ambulance. After the close of the Korean War, Major Anderson chose to stay in the Army. He was posted to Germany in 1956, and at the time of his death was head of the Royal Canadian Army Medical Corps.

Major Anderson had always been a great athlete and was prominent in discus throwing and other field sports. On April 24, he competed in a Canadian Army athletic meet in which he won three events. The following morning, although he was not feeling well, he got in his car to drive a distance of 20 miles. It was during this drive that he was seized with an acute coronary attack which caused his car to leave the road.

Major Anderson took an active interest in all community affairs. For a number of years he headed the Digby Recreation Commission, and it was through his efforts that an artificial rink and a club-house were established in Digby.

He is survived by his widow, the former Joyce Atherton, R.N., formerly of Amherst, and two children, Leslie, 11, and Ian, 10. His mother, Mrs. F. L. Anderson, of Digby, also survives him, as does a sister, Jean, Mrs. T. L. Rogers of Yarmouth.

DR. GEORGE RAYMOND BABY, 65, a general practitioner in Hamilton, died there on May 9. He was born in Quebec and graduated from McGill University in 1915. He served in World War I with the Nineteenth Field Ambulance. Dr. Baby set up practice in Hamilton after the war.

He is survived by his widow, a son and a daughter.

DR. JAMES WARREN BARTON, 79, examining physician for the Ontario Athletic Commission for more than 20 years, died in Toronto on May 5. He was born in Toronto and graduated from Queen's University, Kingston, later studying at the University of Georgia. Dr. Barton was physical director for the YMCA in Kingston, Baltimore, Md., and Atlanta, Ga. He was second in command of the base hospital unit at the old Toronto General Hospital in World War I. For over 35 years he was a newspaper columnist on medical subjects, and was author of the column "That Body of Yours". For 25 years he was physical director at the University of Toronto, and was an official of the Toronto Police Games and CNE sports for many years.

Dr. Barton is survived by two daughters.

DR. ARTHUR BESNER, 45, died in Maniwaki, Que., on May 7. He was born in Maniwaki, and graduated from Laval University, Quebec, in 1940. He began to practise in Maniwaki the same year.

Dr. Besner is survived by his widow and one son.

DR. JOHN NORTHCOTE DECK, 82, a pioneer South Pacific missionary doctor, died on May 10 in Toronto. He was born in London, England, and graduated from the University of Sydney, Australia. In 1908 he began to work as a medical missionary and captain of a missionary schooner for the South Seas evangelical mission in the British Solomon Islands. He was made a Fellow of the Royal Geographical Society for his exploration of Rennell Island. Dr. Deck returned to England in 1927 to stimulate interest in missionary work. He had lived in Toronto since 1942.

DR. CALEB T. HILTON, a B.C. pioneer doctor, died in Port Alberni, B.C., on May 10. He was born in Wigan, England, and graduated from London University and Guy's Hospital in 1875. He went to Port Alberni in 1908 and practised there until 1945. Dr. Hilton was one of the founders of the district's first hospital in 1913. During World War I he served with the Royal Canadian Army Medical Corps.

He is survived by a son and three daughters.

DR. HAROLD EDWIN KILLAM, aged 79, died suddenly on April 24, of a heart attack. Dr. Killam had practised for 40 years in Kentville, N.S. In his early years he had gone to Provincial Normal College in Truro, and after graduation he taught school for four years. He then enrolled at the Dalhousie Medical College, Halifax, where he graduated M.D.C.M. in 1906.

He held a number of appointments in Kings County. He was the Medical Health Officer, and visiting physician to the Kings County Hospital at Waterville. He was also the medical officer for the Kings County Militia Unit at Aldershot.

Dr. Killam always had shown a keen interest in church affairs. He was a member of the Wesley Knox United Church, and was also a member of the church choir for many years. Always interested in the apple industry, he became a well-known fruit grower himself, and his apple orchards were known as among the finest in the Annapolis Valley.

Surviving him besides his widow, the former Ora Louise Webster, are two sons, Fred and Harold of Grafton; three daughters, Margaret (Mrs. C. Atwood), Toronto; Joyce (Mrs. M. T. Barkhouse), Montreal; and Kathleen, wife of Dr. L. E. Cogswell, Berwick; and 18 grandchildren. W.K.H.

DR. LEON LABARRE, 49, died in Montreal in May. He was born in Montreal and graduated from the University of Montreal in 1934. He established a practice in Varennes, Que., and for many years was its mayor.

Dr. Labarre is survived by his widow, six sons and one daughter.

DR. GEORGE EVERETT LEARMONTH died in the Colonel Belcher Hospital, Calgary, on May 10. He was 81 years of age and had practised continually in Calgary since 1918. He was born and educated in Montreal, graduating from McGill University in 1901. In 1904 he moved to High River, Alberta, where he practised for 12 years before joining the Canadian Army Medical Corps in World War I. Dr. Learmonth was a life member of the Canadian Medical Association, Alberta Division, and for several years was Chairman of the Committee on Archives. He was one of the early Alberta doctors honoured by the Division during the province's jubilee celebrations.

Dr. Learmonth is survived by his widow, a daughter and two sons.

DR. ABRAHAM K. MALOUF, 78, a founder of the Syrian-Lebanese colony in Montreal, died in that city in May. He was born in Syria, and graduated from the University of Montreal in 1901. He joined the health department of the city, and was medical inspector of schools from 1906 until 1942.

Dr. Malouf is survived by a son and a daughter.

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DR. P. WILFRED PATTERSON, 59, a physician in Grand Rapids, Mich., for 31 years, died there in April. He was born in Parkhill, Ont., and graduated from the University of Western Ontario. He served his internship in the Great Ormond Street Children's Hospital, London, England.

Dr. Patterson is survived by his widow, one daughter and two sons.

DR. HENRY MATTHEW STEPHENS, 87, a Regina physician since 1904, died there on May 9. He was born in Etobicoke Township, York County, Ont., and graduated from Trinity Medical College, Toronto, in 1901. He practised for three years in Lennox County, Ont., before moving to Regina. Dr. Stephens specialized in obstetrics, although maintaining a general practice. For many years he was president of the Regina School of Nurses.

DR. RUSSELL R. STRONG of Grand Falls, Newfoundland, died suddenly of heart disease on May 6, at the early age of 44. He was born in St. John's and received his preliminary education there. He graduated in medicine at Dalhousie University in 1938 and, following internship, he returned to his native province and served on the hospital ship *Lady Anderson*. He entered practice at Millertown and subsequently moved to Grand Falls, where he became a leader in the professional and civic life of that community. He did much to promote sports and was the founder and the first President of the Grand Falls Athletic Association. An active member of the Newfoundland Division since its inception, he was Vice-President at the time of his untimely death. He is survived by his widow and two sons, to whom our sympathy is extended. A.D.K.

DR. CLIFFORD TAYLOR, a Toronto ophthalmologist, died in May. He was born in Toronto and graduated from Ohio State University. He served overseas for four years during World War I. During World War II Dr. Taylor did research and experimental work in glass with the National Research Council, Ottawa. For 28 years he worked at the old Christie Street Hospital for veterans. He was a Fellow of the Royal College of Science, the American Academy of Ophthalmology and the American Academy for the Advancement of Science.

DR. MORRIS ZELDIN, 51, a staff member of New Mount Sinai and Northwestern General Hospitals, died in Toronto in May. He was born in Toronto, and graduated from the University of Toronto in 1933. In World War II he served with the Medical Corps.

Dr. Zeldin is survived by his widow and two daughters.

PROVINCIAL NEWS

SASKATCHEWAN

A new admission policy for provincial nursing homes will be implemented for the new Regina Nursing Home, as soon as existing commitments have been met.

The primary intent of the entire provincial nursing homes program is to provide care for those persons needing, as a minimum requirement, skilled nursing which patients cannot get elsewhere on a continuing basis and which local communities ordinarily cannot be expected to provide. This would include patients requiring bed care or wheelchair care, and others who require intermittent skilled nursing care on a long-term basis.

Under the new policy each person applying for admission would be required to supply the Department of Public Health with comprehensive social and medical reports. After a preliminary screening, if the applicant appeared to be eligible, a comprehensive medical examination would be requested, the cost of this examination to be borne by the government.

An Admission Screening Committee would determine eligibility for care in the Government Nursing Home, and establish priorities for admission in three general categories—those needing continuous care on an urgent basis; those needing continuous care, but where there is not urgency; and those needing intermittent care.

The Admission Screening Committee would consist of a physician named by the Department of Public Health, a social worker, and a Nursing Homes representative from the Department of Social Welfare and Rehabilitation.

Regina Grey Nuns' Hospital will celebrate, this summer, 50 years of service to the sick.

A five-day program to commemorate the Golden Jubilee begins June 24, with a parade of nurses to the Holy Rosary Cathedral, for celebration of High Mass. The nurses will be joined by other hospital employees and the Knights of Columbus, and they will take part in the procession, which will move along Dewdney Avenue. A banquet for some Regina citizens will end the day.

Celebrations will continue on the following four days, the highlight being a pageant to be presented by the nurses. There will be a day for the public, a day for patronesses, and a number of teas and luncheons, which have been arranged for the jubilee program.

In 1907 the Grey Nuns purchased a small private sanatorium on Angus Street, and construction at the present site of the hospital began in 1910.

Patients come to the Grey Nuns' Hospital from all parts of Saskatchewan, neighbouring provinces, and the bordering states of the United States.

In 1956, 12,567 inpatients and 6553 outpatients were treated. Many more were referred to the Allan Blair Memorial Clinic, which along with the Provincial laboratories is housed within the hospital.

Dr. Benjamin Hargarten from Saskatoon was elected president of the Saskatchewan Chapter of the College of General Practice of Canada, at a business session held in connection with the First Annual Scientific Convention in Regina during April.

Dr. Hargarten will succeed Dr. A. J. Wasylenki of Regina as president. Other officers elected were: Dr. G. W. Kinsman, Saskatoon, provincial secretary; Dr. A. B. Gonor, North Battleford, provincial treasurer; and Dr. I. W. Bean, Regina, as provincial representative to the National Board of Representatives of the College.

It was decided at the business meeting that the Second Annual Scientific Convention would be held next year in Saskatoon.

The ninth annual banquet of the Saskatchewan Psychiatric Nurses Association was held in Weyburn during April.

During the week of May 6, a refresher course, celebrating St. Paul's Hospital jubilee year in Saskatoon, was held in the lecture room of St. Paul's Nurses' Residence, under the co-chairmanship of Dr. D. M. Baltzan, Chief of Staff, and Dr. F. W. Rosher, President of the Medical Staff.

The visiting speakers from outside Saskatoon were: Dr. R. Farquharson, Professor of Medicine, University of Toronto; Dr. H. Medovy, Professor of Pædiatrics, University of Manitoba; Dr. M. Nickerson, Professor of Pharmacology, University of Manitoba; Dr. C. V. Ward, Associate Professor of Obstetrics and Gynæcology, McGill University; Dr. M. Bowering, Regina; Dr. C. Crosby, Regina; Dr. A. Goodfellow, Regina; Dr. J. G. McCarroll, Moose Jaw; Dr. D. C. McEwan, Regina; and

Dr. P. Mousseau, Edmonton. In addition, an active part was taken in the program by many Saskatoon physicians.

The Saskatchewan Department of Public Health this year expects to offer several bursaries for undergraduate university training in physical therapy, occupational therapy, and combined physical and occupational therapy.

President W. P. Thompson of the University of Saskatchewan has announced that plans are being prepared for construction of three new University buildings, but warned that unless more outside help was forthcoming, the University might have to take stringent measures towards controlling the expected sharp increase in student population.

In his report to the University's 46th Annual Convocation, President Thompson stated that the Provincial Government had authorized the University to proceed with preparation of plans for the erection of an Animal Husbandry building, a Biology building, and an Arts building. It is expected the first will be completed during 1958, and the other two in 1959, in time for the University's Golden Jubilee celebrations. G. W. PEACOCK

MANITOBA

It was pleasing to have Dr. W. Donald Ross, Associate Professor of Psychiatry, University of Cincinnati, address the Winnipeg Medical Society on April 10 on industrial psychiatry. He is a graduate of the University of Manitoba, which he represented on debating teams as an undergraduate. He is the author of a book on industrial psychiatry.

Dr. John F. S. Hughes has opened an office for the practice of internal medicine at 326 Medical Arts Building, Winnipeg.

Dr. Stephen Kovacs has been appointed to the medical staff of Brandon Sanatorium. He is a graduate of the University of Budapest and has recently arrived from Europe.

Following the annual meeting of the Winnipeg General Hospital on April 24, scrolls were awarded to 18 doctors who have served the hospital for more than 25 years. A study had shown that the honorary attending medical staff had contributed $400,000 in service to public ward patients. Doctors honoured were G. L. Adamson, L. G. Bell, A. R. Birt, C. W. Burns, F. T. Cadham, N. L. Elvin, A. M. Goodwin, J. A. Gunn, M. S. Hollenberg, H. D. Kitchen, M. R. MacCharles, A. T. Mathers, H. Medovy, R. B. Mitchell, H. D. Morse, P. H. T. Thorlakson, N. H. Warner and O. S. Waugh.

Dr. Robert F. Yule, The Pas, retired on April 30 as medical officer of Indians north of 53'. He and his wife will go to the Pacific Coast. Dr. Yule graduated M.D. from the University of Manitoba in 1920 and practised at Kenton before assuming his mission to the Indians 16 years ago. His patients included Crees and Chipewyans in the Churchill area and Eskimos. Dr. Harold Colburn will succeed him.

Dr. John N. R. Scatliff has been appointed medical director of Misericordia Hospital in succession to the late Dr. Owen C. Trainor, M.P. A graduate of St. Bartholomew's Hospital, London, and Toronto (D.P.H.), Dr. Scatliff has engaged in municipal and public health practice since coming to Canada. At present he is administrator of the St. James, St. Vital, Fort Garry, Charleswood Health Unit. He is a past vice-president of the Astronomical Society of Canada.

Dr. and Mrs. W. A. Bigelow of Brandon recently celebrated their golden wedding anniversary. Dr. Bigelow started one of the earliest surgical clinics in Western Canada.

The annual meeting of the Winnipeg Medical Society was held at the Medical College on May 10.

Reports indicated that the Society is flourishing. There are 465 members. The general fund shows a credit balance of over $8000; the library fund $1185; the benevolent fund of over $6000. It was recommended that overtures be made to the Manitoba Medical Association to have the benefits of a benevolent fund made available to all Manitoba doctors.

A certificate was presented to Dr. A. R. Birt, immediate Past President. Life Memberships were presented to Doctors H. D. Morse, James Prendergast, W. M. Musgrove and W. F. Abbott.

Dr. Earl Stephenson, president, gave an address on stones in the urinary tract, illustrated with photographs in colour made by himself and with x-ray films.

The election of officers resulted as follows: President, Dr. Athol Gordon; Vice-President, Dr. J. L. Downey; Secretary, Dr. J. A. Swan; Treasurer, Dr. R. L. Cooke; Trustee, Dr. D. L. Kippen. ROSS MITCHELL

ONTARIO

Dr. John Hamilton and Dr. Carl Burton, Toronto, and Dr. J. C. Paterson, London, attended the first Wisconsin Conference on Work and the Heart held at Marquette University, Milwaukee, in May.

Over 500 medical librarians attended the 57th annual meeting of the Medical Library Association which was held in New York in May. Ontario medical librarians attending were Miss Olga Bishop, University of Western Ontario; Miss Eileen Bradley, University of Toronto; Miss Ruth Briggs, Connaught Medical Research Laboratories; Miss Hazel Williamson, Department of Pathology, Toronto; Miss Margaret Wright, Hospital for Sick Children; and Miss Marian Patterson, Toronto Academy of Medicine.

Miss Patterson gave a paper on "Discarding, a problem in librarianship" at the Medical Society Group meeting.

The second Murray Gottlieb award for the best essay on some phase of American medical history, written by a medical librarian, has been granted to Miss Marian Patterson.

The highest international nursing award, the Florence Nightingale Medal, has been awarded to Miss Helen McArthur, national director of nursing services of the Canadian Red Cross Society, by the International Committee of the Red Cross, Geneva. The medal, bearing the likeness of Florence Nightingale, was established in 1912, and is given for outstanding contributions to the development and prestige of the profession. Miss McArthur served 18 months in Korea where she was adviser to the Korean Red Cross and was responsible for channelling all relief material forwarded by societies throughout the world.

Dr. William Boyd, Toronto, was awarded the William Gearhard Medal at the centenary meeting of the Philadelphia Pathological Meeting. This medal is not an annual award but is presented only for distinguished work. Among former recipients were Dr. William H. Welch (1925), Dr. Theobald Smith, Dr. F. d'Herelle, Dr. Eugene L. Opie, Dr. Simon Flexner, Dr. A. N. Richards, Dr. Frank C. Mann, Dr. George H. Whipple,

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Dr. Howard Karsner, Dr. Paul R. Cannon, Dr. Jean Oliver, and Dr. R. Philip Custer (1955).

The $2,500,000 wing of the Oshawa General Hospital was opened recently by Premier Leslie Frost. It is the fifth major addition since the hospital opened 47 years ago. The 112-bed addition provides the last word in technical and architectural hospital facilities.

Dr. Hagar Hetherington was elected President of Toronto Academy of Medicine at its 50th annual meeting. Dr. R. C. Laird was elected Vice-president, Dr. W. E. Ortved Honorary Treasurer and Dr. G. F. Culnan Honorary Secretary. The membership is 2061.

The provincial government in co-operation with the Ontario Medical Association is conducting a survey of handicapped persons to see whether more would benefit from vocational training. The first survey made from a selection of 100 doctors in Metropolitan Toronto and the counties of Kent, Simcoe, Hastings and Carleton has already resulted in several hundred cases being referred.

In addition to the cost of training, the plan provides for maintenance costs while the training goes on. Persons suffering from the after-effects of tuberculosis make up 54.7% of the trainees.

Toronto Western Hospital's $4,510,000 building fund was oversubscribed by $701,704. A 76-bed wing will be added, as well as a 90-bed addition to the nurses' residence and a seven-storey structure north of the private patients' pavilion.

The cornerstone has been laid for the new Grace Hospital of the Salvation Army, Toronto. This will be the first all-obstetrical hospital built in Canada. Accommodation is for 125 adults and 88 infants. It will cost more than $2,000,000.

Dr. A. J. B. Goldsmith of Middlesex Hospital, London, has been appointed visiting professor in the Department of Ophthalmology, University of Toronto, on an exchange agreement initiated last year between the two institutions. Dr. Goldsmith is surgeon-oculist to Her Majesty's Household. Dr. Robert Janes has just returned from a month's term as visiting professor of surgery at the Middlesex Hospital.

At a Convocation held by the College in Boston on April 10, Dr. Elliot M. Heller of Toronto was made a Fellow of the American College of Physicians.

This year's convention of the Gallie Club was held in Great Britain. About 25 members from all parts of Canada made the trip. On June 10 they visited St. Thomas's Hospital, London, and on June 11 the Middlesex, and on the same day they heard the Henry Lecture at the Royal College of Surgeons given by Mr. L. W. Plewes, F.R.C.S., on "The surgeon and industry". Mr. Plewes, a brother of Dr. Burns Plewes, Toronto, is chief surgeon at Luton and Dunstable Hospital, Bedfordshire. That evening Dr. Gallie was host at a dinner at the Royal College. The silverware of the Royal College was left to it by Sir John Bland Sutton and is of Egyptian motif, featuring cats, and other animals.

On June 12 they met at the Radcliffe Infirmary, Oxford, and on June 14 at the Royal Infirmary, Edinburgh. That evening the annual Gallie Club Dinner was held at the Royal College of Surgeons; on the following day a plaque was presented by Dr. R. I. Harris to mark the room where Lister and Syme worked. In the evening Mr. Roy Thompson, Canadian proprietor of *The Scotsman*, was the dinner host.

Among those making the trip were: Dr. E. H. Botterell, Dr. Ian B. Macdonald, Dr. Charles J. Robson, Dr. Donald R. Wilson, Dr. Burns Plewes, Dr. James E. Bateman, Dr. David Bohen, Dr. Marjorie Davis, Dr. Jessie Gray, Dr. Harry Joynt, Dr. Robert Laird, Dr. Frank Mills, Dr. Keith Welsh, and Dr. William Kerr, all of Toronto; also Dr. Fred Wigmore, Moose Jaw; Dr. John Stewart, Peterborough; Dr. Harold Mowat, Sudbury; Dr. H. S. Anderson, Edmonton; Dr. David Bean, Kitchener; Dr. James Francis, Calgary; Dr. Charles Greig, Sault Ste. Marie; Dr. Alan Lane, Hamilton; Dr. Angus McLachlin, London; Dr. George Walker, Sudbury.

The only member practising in Great Britain is Mr. Kent Harris, head of the department of chest and cardiac surgery, St. Thomas's Hospital, London.

LILLIAN A. CHASE

QUEBEC

Dr. Aurèle Beaulner, a graduate in medicine of the University of Montreal and currently a fellow at Oxford University, England, has been named "scholar of medical science" by the John and Mary R. Markle Foundation. He will be assistant professor at the University of which he is a graduate, on the basis of a $30,000 grant to the university over five years. As is now well known, under the Foundation plan, $6000 annually for five years will be appropriated towards the support of each appointee in the school where he will teach and carry on research.

Dr. Ian Stevenson, a 1943 graduate in medicine of McGill University and intern at the Royal Victoria Hospital, has been named professor of neurology and psychiatry and chairman, department of neurology and psychiatry, University of Virginia Medical Center, Charlottesville, Va. He is a native of Montreal.

On April 11, Dr. Murray Stalker, medical superintendent of the Barrie Memorial Hospital at Ormstown, Quebec, reported at the annual meeting that the development of community hospitals may be the answer to the problem of disappearing medical service in the rural areas of Canada. Because of the development of the hospital and that of the Huntingdon County Hospital, 12 physicians are now in the area where formerly there were only four.

The great problem today, however, is to finance such hospitals. The basic problem is to provide a quality of service to all, regardless of ability to pay. More and more people are unable to pay the total cost in hospital. A public bed that had a basic charge of $2.50 in 1939 now costs $7.50. The average cost per day in 1941 was $4.48, and is now $15.54. Increasing inflationary costs and the difficulty of getting sufficient trained staff add to this strain.

The annual meeting of the Montreal Neurological Institute was held on May 16 under the chairmanship of Dr. F. Cyril James, principal and vice-chancellor of McGill University. The reports of Dr. Wilder Penfield, director of the Institute, and of the departments were presented. Dr. Penfield, in expressing admiration for the Massey Commission report and its implementation, pointed out that, in spite of its title, it concerns itself with arts, letters and culture, but largely ignores the sciences. He emphasized that certain conditions must be fulfilled if higher education is ever to flow as it should in Canada. Our institutions must have stability and independence. They need financial assistance far in excess of the present level of support.

Following the meeting, Dr. Herbert Gasser, director emeritus of the Rockefeller Institute of Medical Research, New York, delivered the Hughlings Jackson Lecture. Dr. Gasser won the Nobel Prize in 1954 for his work on nerve impulses.

The Life Insurance Medical Research Fund has announced that research institutions in Montreal have been awarded $31,900 for heart disease work in 1957. One grant of $13,200 is for the study of the hormone aldosterone in hypertension, at the Hotel Dieu. The other grant, for $18,700, is for the study of low sodium intake effects on aldosterone secretion in hypertension.

The first joint meeting of the Canadian Urological Association and the British Association of Urological Surgeons was held at the Montreal General Hospital on May 13 to 15. Some 50 surgeons from Britain, Ireland, Sweden, India and Australia joined well over a hundred leading Canadian urologists for this three-day meeting.

Dr. Arthur C. Curtis, professor and chairman of the department of dermatology and syphilology, University of Michigan, addressed the Montreal Medico-Chirurgical Society on April 26 on "The common mole and disturbances of pigmentation". The thesis, so long held by Masson, that melanin pigment is a derivative of the neural crest and hence exists in dendritic cells present in the neural crest and which later migrate to the junction area of the skin, was developed. The genetic aspect of pigmentation, especially the studies of Gordon, was illustrated. He discussed in some detail the chemical relationship of pigmentation in human beings. Newer facts relating to pigmentation, such as the relationship of the sulphydrils, nascent oxygen and copper as a catalyst, were presented. Pigmentation in the human organism is under a carefully controlled balance between the melanin stimulating hormone of the pituitary and adrenal glands, and the various agents in the skin, such as nascent oxygen, copper and the sulphydril groups.

Dr. and Mrs. J. J. McGovern were guests of honour at the Annual Dinner of the Montreal Dermatological Society held in the Queens Hotel on April 27. Dr. McGovern, who was a founding member and who celebrated his eighty-first birthday on April 29, was promoted to emeritus membership in the Society. A suitably inscribed silver cigarette box was presented to him to mark the occasion. Dr. McGovern is still enjoying active practice in this city.

Dr. Arthur C. Curtis, professor of dermatology and chairman of the department of dermatology of the University Hospital, Ann Arbor, Michigan, addressed the members of the Montreal Dermatological Society at their Annual Meeting held in Notre-Dame Hospital, Montreal. After a brief clinical presentation, Dr. Curtis outlined the various research projects which are taking place at the University of Michigan in the field of dermatology.

Professor Pierre Masson, head of the pathology department of the University of Montreal, who has been a member of the faculty of medicine of this university for the last thirty years, has recently been awarded the title of Officer of the Legion of Honour by the French Government. Dr. Masson was born in France and was associated with the Pasteur Institute in Paris for ten years. Before coming to Canada, he was professor of pathology at the School of Medicine of the University of Strasbourg.

A. H. NEUFELD

NOVA SCOTIA

Dr. W. A. Curry, professor of surgery, Dalhousie University, has retired from the staff of the Children's Hospital. Following his retirement he was appointed to the honorary consulting staff. Dr. E. F. Ross was appointed surgeon-in-chief of the Children's Hospital on Dr. Curry's retirement. Dr. Jack Acker was appointed chief of the reorganized orthopædic service, with Dr. B. F. Miller as associate. Dr. J. H. Charman was appointed assistant surgeon to the general surgical staff.

"Ours the Wind Against the Eyes"—Rupert Brooke

The pilot and flying surgeon, W. O. Coates of Amherst, left his home during the first week of March in the company of Mr. Norman Carruthers of Moncton and flew to Miami, Florida. From there, Dr. Coates took off by himself and flew his plane from Key West, Florida to Havana.

Whilst in Havana he attended the medical meeting of the Flying Physicians' Association, of which he is a member. On his return to the mainland, he continued his flight to Toronto where he attended the Sectional meeting of the American College of Surgeons. Altogether, he flew a distance of over 6000 miles within a three-week period.

WALTER K. HOUSE

PRINCE EDWARD ISLAND

The P.E.I. Orthopædic Centre is a government institution established in 1955 for poliomyelitis and tuberculous bone cases requiring orthopædic treatment. The patients are admitted on recommendation of the outpatient clinic, old cases being referred by their family physician.

The east end of the provincial sanatorium was remodelled in order to adapt the space to the treatment of orthopædic patients. The old polio clinic which was on the lower floor was completely renovated. A new physiotherapy department was established with a swimming pool for physiotherapy, 17′ x 13′ with five different levels from 2′ to 5′. There is a gymnasium 35′ x 20′ which is fitted with modern physiotherapy equipment for polio and other types of orthopædic cases; this equipment consists of a walker, wheel for exercise of the shoulder, pulley for exercise of the shoulder, cervical traction, standard orthopædic tables for exercises, stationary bicycle, practice stairs and wall bars for scoliotic patients. There is also a hydrotherapy room with whirlpool and shower. On the same floor there is a plaster room, as well as a small room fitted with equipment for the repair and adjustment of shoes and braces. There is an outpatient department consisting of a doctor's office, examining room, waiting room with accommodation for approximately 20 patients, and a secretary's office.

There is space on the second floor for 28 patients; the children's section, accommodating 14 patients, is completely separate from the adult section. There is a room for postoperative care, where the patient usually stays for six or seven days after surgery. The schoolroom is also located on this floor; there is a yearly enrolment of 28 pupils and regular classes are held—Grades 1 to 10.

Admissions to the Centre at the present time are confined to poliomyelitis cases and cases of bone tuberculosis without active disease of the chest.

The medical staff at the Orthopædic Centre consists of an orthopædic surgeon in charge, a consulting chest specialist, a consulting general surgeon and an anæsthetist. The nursing staff consists of a matron, seven registered nurses and seven nursing assistants, and three orderlies. There are two physiotherapists, one secretary, one schoolteacher and one man in charge of brace and shoe repair and adjustment.

T. GENCHEFF

WHO AND CANCER RESEARCH

It has been decided by the World Health Assembly that WHO should undertake an important research program in the field of epidemiology of cancer, in the hope that comparative study of variations between cancer types in different countries may yield a clue to the origin of this disease.

FORTHCOMING MEETINGS

CANADA

NINTH INTERNATIONAL CONGRESS OF RHEUMATIC DISEASES, Toronto, Ontario. (Ninth International Congress of Rheumatic Diseases, P.O. Box 237, Terminal "A", Toronto, Ont.) June 23-28, 1957.

CANADIAN ANÆSTHETISTS SOCIETY, Saskatoon, Sask. (Dr. Christopher J. Kilduff, University Hospital, Saskatoon, Sask.) June 24-26, 1957.

CANADIAN TUBERCULOSIS ASSOCIATION, 57th Annual Meeting, Vancouver, B.C. (Canadian Tuberculosis Association, 265 Elgin Street, Ottawa, Canada.) June 24-30, 1957.

UNITED STATES

INTERNATIONAL COLLEGE OF SURGEONS, 22nd Annual Congress and Convocation of the United States and Canadian Sections, Chicago, Ill. (Dr. Karl A. Meyer, Secretary, 1516 Lake Shore Drive, Chicago 10, Ill.) September 8-12, 1957.

OTHER COUNTRIES

TWELFTH INTERNATIONAL CONGRESS ON OCCUPATIONAL HEALTH, Helsinki, Finland. (The Congress, Työterveyslaitos, Haartmanikatu 1, Helsinki-Tööiö, Finland.) July 1-6, 1957.

INTERNATIONAL SOCIETY OF CLINICAL PATHOLOGY, Third Congress, Brussels, Belgium. (Professor M. Welsch, Secretary-General, Service de Bactériologie et de Parasitologie, Université de Liège, 32 Blvd. de la Constitution, Liège, Belgium.) July 7-14, 1957.

INTERNATIONAL CONFERENCE ON THE ENDOCRINE ASPECT OF BREAST CANCER, Glasgow, Scotland. (A. P. M. Forrest, Ch.M., F.R.C.S., Department of Surgery, Western Infirmary, Glasgow, W.1, Scotland.) July 8-10, 1957.

FOURTH INTERNATIONAL CONFERENCE ON POLIOMYELITIS, Geneva, Switzerland. (International Poliomyelitis Congress, 120 Broadway, New York 5, New York.) July 8-12, 1957.

FOURTH INTERNATIONAL CONGRESS OF GERONTOLOGY AND GERIATRICS, International Association of Gerontology, Merano, Italy. (Dr. Scardigli, Societa Italiana di Gerontologia, 85, Viale Morgagni, Florence, Italy.) July 14-21, 1957.

FIRST INTERNATIONAL CONGRESS OF NEUROLOGICAL SCIENCES, Brussels, Belgium. (Dr. Ludo van Bogaert, Secretary-General, First International Congress of Neurological Sciences, Institut Bunge, 59, rue Philippe Williott, Berchem-Anvers, Belgium.) July 21-28, 1957.

11TH INTERNATIONAL CONGRESS OF DERMATOLOGY, Stockholm, Sweden. (Dr. C. H. Flodén, Secretary-General, Dermato-Dermatologiska Kliniken, Karolinska Sjukhuset, Stockholm 60.) July 31-August 6, 1957.

WORLD FEDERATION FOR MENTAL HEALTH, 10th Annual Meeting, Copenhagen, Denmark. (Secretary General, World Federation for Mental Health, 19 Manchester Street, London, W.1, England.) August 11-17, 1957.

SECOND WORLD CONGRESS OF PSYCHIATRY, Zurich, Switzerland. (Professor Dr. Med. Jakob Ulyrsch, Lenggstrasse 28, Zurich 8, Switzerland.) September 1-7, 1957.

SECOND EUROPEAN CONGRESS OF AVIATION MEDICINE. Stockholm, Sweden. (Dr. Olle Höök, Secretary General of Congress, Flygvapnet, Stockholm 80, Sweden.) September 16-18, 1957.

WORLD MEDICAL ASSOCIATION, 11th General Assembly, Istanbul, Turkey. (World Medical Association, 10 Columbus Circle, New York 19, N.Y.) September 29-October 5, 1957.

BOOK REVIEWS

MEDICAL NEGLIGENCE, Being the Law of Negligence in Relation to the Medical Profession and Hospitals. The Right Hon. Lord Nathan, and Anthony R. Barrowclough. 217 pp. Butterworth & Co. (Canada) Ltd., Toronto, 1957. $8.75.

Medical professional malpractice and negligence, whether commoner now than previously, at least seem to be stimulating more people to write about them. The author of this book writes well and the book is a valuable addition to the literature. Its scope is wide; its material is well presented; its style is interesting and readable; its references are many. The references, predominantly to British cases, include many Canadian as well as South African and Australian cases; a few American decisions are discussed; many of the cases are the precedents for the present-day judgments. Legal reasoning keeps searching for basic principles which can be applied widely; more and clearer reasoning modifies the principles, and changes in medical knowledge and in relationships between hospitals and doctors force changes in principles. How different are the conclusions reached is illustrated in the Hillyer v. Governors of St. Bartholomew's Hospital case and in the Gold v. Essex County Council case which attempt to define the relationship between doctors and hospitals. Canadian hospitals and doctors should read and understand this change in legal responsibility. The significance and implications of the statement that the ". . . view, for example, that nurses pass under the control of the surgeon during an operation to such an extent as to cease to be the servants of the hospital authority must certainly be regarded as erroneous," may perhaps not be clearly understood by hospitals or doctors. The underlying legal reasons are given for many of the decisions; the law has reached some conclusions very slowly and the reasons the conclusions were reached are interesting and sometimes surprising. For many problems still undecided, the reasoning to date is given.

Every doctor who has some interest in the legal aspects of his medical work will find his interest both piqued and satisfied by this book.

THE FAT OF THE LAND. Vilhjalmur Stefansson. 329 pp. Enlarged ed. of "Not By Bread Alone". Brett-Macmillan Ltd., Toronto, 1956. $5.00.

This book by Dr. Stefansson is an enlarged edition of his previous work entitled "Not By Bread Alone". The present volume has two interesting comments by Dr. Frederick Stare, Professor of Nutrition, Harvard School of Public Health, and Dr. Paul Dudley White, the famous Boston cardiologist.

When Stefansson and Karsten Andersen went on their famous meat diet for one year in 1928, the medical profession, physiologists and dietitians strongly held the view that for good health everyone should have the traditional balanced diet, every day and all the time. This view was shown to be erroneous. The two experimental subjects were perfectly well and healthy on a diet of meat and fat. Let it be noted that the human animal is most adaptable, and that a fair number of allegedly "scientific" facts about diet are based on what may be called pseudo-scientific folklore and not on real facts. This might come as a shock to dietitians and physicians, but they should re-examine some of these "facts" and they will find that many of them are extremely tenuous.

The present interest in fats and coronary thrombosis should lead to more experiments, similar to the classical one of Stefansson. He has lived on a high meat and fat diet with plenty of hard exercise and he is healthy and vigorous, but quite lean, at the age of 77. The question of exercise may be crucial in terms of recent

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experimental work carried out in Dr. Stare's department. Furthermore, Eskimos eat seal oil, fish and blubber, which are high in unsaturated fatty acids. Incidentally, no one really knows much about Eskimo pathology. There are less than 10,000 of these people in the Canadian Arctic and there have been very few autopsies on them.

The section on scurvy is most interesting, especially the historical aspects. Fresh meat may not contain much ascorbic acid, but from Stefansson's experience and from historical evidence, it does prevent scurvy. Do we really know how much iron ascorbate is contained in the different cuts of meat, or how much dehydroascorbic acid? Parenthetically, in regard to the 75 mg. of ascorbic acid recommended as a daily intake by the United States National Research Council, how much of this recommendation is based on real fact?

And a word is needed on pemmican, this erstwhile staple of Canadian exploration. This food was tested by the Canadian Army during the last war, and it was found wanting. But was this very brief test adequate? What would have happened if the troops concerned had become properly accustomed to the consumption of this very concentrated food before starting the experiment?

This book should be read by all those who are interested in nutrition and dietetics. It will give them quite a different orientation, and it should result in a great measure of critical self-examination. How much of our official views on dietetics are based on purely our own customs, the prestige values of certain foods, vague concepts of "white superiority", oft-repeated scientific folklore, and how much on soundly interpreted scientific observation?

BRITISH MEDICAL BULLETIN, Vol. 13, January 1957: Physiology and Pathology of the Kidney. Edited by Robert Platt. 74 pp. Illust. The Medical Department, the British Council, London, England; Oxford University Press, Toronto, 1957. $3.25.

This symposium is written by clinicians and is concerned more with the applied physiology and pathology of the kidney than with pure physiological considerations. It is fitting that the foreword to the symposium should be written by Dr. Robert Platt, the new President of the Royal College of Physicians of London, whose interest in kidney disease is well known. Dr. Platt points out the shift in emphasis in the study of kidney disease from that of the kidney's efficiency as an excretory organ to its role as a homœostatic organ. He also emphasizes the fact that the worker on kidney disease is no longer isolated; his problems touch many other fields, such as those of endocrinology, metabolism, obstetrics, orthopædics, neurology and psychiatry.

The symposium begins with a review by McCance and Widdowson of their work on renal function in the newborn, with special reference to the studies on piglets showing the effects of food composition and of growth on the homœostasis in the newborn. Black and Emery describe work leading to the conclusion that the urinary potassium is substantially the result of tubular secretion and not of glomerular filtration. Among the many other interesting contributions to this symposium are two on potassium deficiency and the kidney, in which the functional and morphological changes in the distal tubule, as well as the histochemical changes, best seen in the renal medulla, are described and illustrated by photomicrographs. Darmady and Stranack illustrate a technique of microdissection for the study of lesions of the kidney. A summary of recent work on renal aminoaciduria includes sections on cystinuria, galactosæmia and Hartnup disease (hereditary pellagra-like rash with cerebellar ataxia and aminoaciduria). There are several contributions on hypertension, with reference to such topics as the role of the kidney in experimental hypertension and the treatment of hypertension in primary renal disease by hypotensive drugs. The obscurities of the nephrotic syndrome are discussed, and also those in the pathogenesis of urinary stone formation. There are contributions on the newer techniques of renal-angiography and venography. The whole symposium represents a most valuable conspectus of recent work in kidney disorders, and will be of wide value to clinicians in many fields.

GENERAL UROLOGY. Donald R. Smith, University of California School of Medicine, San Francisco. 328 pp. Illust. Lange Medical Publications, Los Altos, Calif., 1957. $4.50.

In the space of 328 pages, Dr. D. R. Smith has compiled an excellent review of urology, complete with x-ray reproductions, many drawings, a small but representative bibliography, and a complete index. The author has shown considerable talent in paring his material down so that only the essentials are included. Each pathological process is organized under various headings including etiology, pathology, clinical picture, and treatment. Of necessity, controversial aspects have been omitted completely, and the material included is precise and pertinent.

The first six chapters are devoted to basic urological subjects. Anatomy, urological symptoms and examinations are briefly reviewed; the latter includes the physical, laboratory, roentgenological and instrumental examinations of importance in urology. Urological lesions are then considered, first on a pathological basis (obstruction, infection, stones, injuries, and tumours) and then on an anatomical basis (neurogenic bladder, perirenal area, kidneys). The final four chapters are devoted to special urological problems: intersexuality, renal hypertension, infertility, and psychosomatic urologic symptoms.

This book is one of a series of medical publications designed for the general practitioner and student and it will admirably complement the other issues. The author has accomplished his purpose well and the student and practitioner are presented with a well-organized and complete treatise on urological problems.

The chapter on neurogenic bladder is especially well done and will be found to be a helpful review of a confusing subject. The excellence of the drawings is well shown here.

The reviewer has no hesitation in recommending this book to the student, general practitioner, or anyone, including the urologist, who is looking for a short, precise, up-to-date review of urology.

VITAMIN B_{12} UND INTRINSIC FACTOR. 1. Europäisches Symposium, Hamburg 1956 (Vitamin B_{12} and the Intrinsic Factor). Edited by H. C. Heinrich, University of Hamburg, W. Germany. 576 pp. Illust. Ferdinand Enke Verlag, Stuttgart, W. Germany, 1957. DM 75.

This volume contains the papers given at the first European symposium on vitamin B_{12} and intrinsic factor, held at Hamburg in 1956. In the foreword the organizers of the symposium, which was held in Hamburg because research on vitamin B_{12} had been going on there since 1951, point out that the title might suggest an extremely specialized theme. This is not so, for vitamin B_{12} must play a fundamental part in biological systems and research in this vitamin must have applications to all sorts of other investigations in general biology and biochemistry. Although the title of the symposium is given in German, it should be noted that at least 50% of the papers were given in English, the remainder being mostly in German, with only two contributions in French. There were eight main subjects, in each of which a number of papers were given: (1) the chemistry and biosynthesis of vitamin B_{12} compounds; (2) the biological activity and biochemical mechanism of action of vitamin B_{12}; (3) intrinsic factor and B_{12} binding factors; (4) assay of the vitamin; (5) the pathogenesis, symptoms and diagnosis of vitamin B_{12} deficiency; (6) the pathological physiology of vitamin B_{12}; (7) vitamin B_{12} in therapy; (8) vitamin B_{12} metabolism and the liver. In addition there is a paper on the spasmolytic and detoxi-

cating effect of vitamin B_{12}; and the symposium ends with a report of the *ad hoc* nomenclature commission set up at the symposium to discuss the nomenclature of vitamin B_{12} compounds. This commission came up with such names as corphyrin, corrin (to designate the fundamental system with 4 pyrrol nuclei joined in a macro ring with three bridge carbon atoms and six conjugated double bonds), corphyrinic acid (corrin with cobalt), corphinic acid and corphinamide, cobamic acid and cobamide. These names must be checked for legal availability and can only be used provisionally until they receive the approval of the International Union of Biochemistry. All those interested in vitamin work will presumably wish to consult this volume, which has been well produced by the Ferdinand Enke publishing house.

OPTICS, THE SCIENCE OF VISION. Vasco Ronchi, National Institute of Optics, Arcetri, Italy; translated by Edward Rosen, City College of New York. 360 pp. Illust. New York University Press, New York, 1957. $10.00.

This book is a translation by an American historian of a text by an Italian professor of physics. The original author was a doctor of philosophy in physics of the University of Pisa who taught as well as carried out scientific and technical work in optics for 40 years.

The translation has been divided into nine chapters, only the last three of which resemble the usual textbook in optics. These three concluding chapters are the most valuable to the student who wishes to understand the derivation of formulæ and optical principles. They refer to the laws of the dynamics of harmonic motion, the propagation of waves over homogeneous surfaces, including Huygens' principle of secondary wave motion and the laws of reflection, refraction and diffraction of waves.

The index is very good and must be used often for reference to any one topic, which is scattered throughout the text in several sections.

The first six chapters are extremely confusing. The author has attempted to combine not only physical factors but also psychological and philosophical matters, none of which are clearly presented. He states that "The aim of optics was to discover the conditions and laws that permitted one to see well. Therefore it should not restrict itself to ascertaining the characteristics of the physical stimulus but should concern itself with the effects of that stimulus on the sense organ and with the consequence in the realm of the mind." He continually criticizes the accepted point of view in optics. For example, "Matter emits radiation which may be absorbed and detected by photoelectric cells via an electrical current, by photosensitive emulsions via a blackening or by the eyes via the perception of light and colour. Only the last is true optics, the first is photoelectricity, the second photography."

In his historical review he mentioned that glasses had been prescribed since the 7th century. The laws of optics and reflection were written and taught as early as the 4th century B.C.

The author's definitions are long and belaboured, making the true point obscure. There is constant reference to astronomy, using stars as examples of "point sources" without making any definite conclusions.

The fifth chapter refers to factors which might affect visual acuity, such as dazzle, brightness or contrast, but their actual effect is difficult to determine from the discussion. The chapter on optical images refers to the rays passing through plane and toric lenses and describes spherical aberration. Although the author supported the wave theory of propagation, he did not believe in rays or photons. He refers to the retinal image as being "the distribution of energy effects on a layer of retina."

All the material in the text is subdivided into 328 sections in 353 pages. Except for titles of nine chapters, there are no headings. There is a great deal of unorganized repetition and skipping about, making it very difficult to follow discussions on microscopes, telescopes and spectroscopes, which are mentioned in many sections in different chapters.

In conclusion, therefore, the reviewer feels that, because of its poor organization, the book is unsuitable for a medical reading room or as reading material for a university course in optics.

EMOTIONAL ILLNESS: How Families Can Help. Karl R. Beutner and Nathan G. Hale, Jr. 158 pp. G. P. Putnam's Sons, New York, 1957. $2.75.

Here is a small book sensitively presenting the problems of mental illness as they affect the relatives of the patient.

Various aspects of emotional illness are discussed in commonsense terms, and the aids available to the patient are cited. The important contribution that the family can make to restore the patient to health is emphasized. Perhaps the keyword in the whole book is "understanding"—understanding the patient and his illness, and the relatives understanding themselves.

Indeed, the most important point stressed, in this reviewer's opinion, is the psychological difficulties which the relatives themselves may have in their relation to the patient, so that they may need psychiatric advice to develop a smooth relationship with the patient, not only during his illness but also in the recovery period.

The need for public enlightenment about mental health is pressing; this book can be recommended to help do just that.

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THE EVALUATION OF THERAPEUTIC AGENTS with Special Reference to the Tranquilizing Drugs. Monograph Series, No. 2, Mental Hospital Service, January 1957. Stewart Wolf, University of Oklahoma School of Medicine. 23 pp. Illust. American Psychiatric Association, Washington, D.C. $1.00.

This little monograph should be read by all engaged in clinical investigation of new therapeutic agents, for it outlines and illustrates, with many experimental and clinical examples, some of the pitfalls and difficulties of the field.

Above all, it deals with the "placebo reactor," and the importance of sociological factors producing an atmosphere, which then produces stress on the experimental subjects, without this stress being perceived as such. This latter point is amply illustrated by Dr. Wolf's data on the changes in sodium, potassium, nitrogen, calcium, and phosphorus balance on a metabolic ward when each nurse, unknown to the patients, was asked which of the doctors she felt were the ablest, which one she liked best, which one treated the patients best; which of the other nurses she liked best, and which one carried out her duties best. This so disturbed the nurses by threatening their security that it produced extraordinary and relatively uniform disturbances in the metabolic balance of the patients under their care, the most striking of which was the alteration in the sodium balance. This striking metabolic result was produced by "the agent here, which was the meaningful situation—unmentioned trouble among the nurses."

This little monograph is full of such experiments, illustrating the importance of factors such as the above-mentioned, and the author has a sophisticated and erudite approach to the problems of evaluating therapeutic agents. The approach to research design and consideration of the number of variables pertinent to a problem becomes therefore a subject of great interest. Many implications as to these last-mentioned factors are found throughout this monograph.

CANADA YEAR BOOK, 1956. The official statistical annual of the resources, history, institutions and social and economic conditions of Canada. Information Services Division, Canada Year Book Section, Dominion Bureau of Statistics. 1280 pp. Illust. Edmond Cloutier, Queen's Printer and Controller of Stationery, Ottawa, 1956. $4.00.

Besides the usual wealth of textual and statistical material, this 51st edition of the *Canada Year Book* (published this year in an attractive new cover) contains special articles on mental health, tuberculosis, and poliomyelitis vaccine. Also included in the chapter on public health, welfare and social security are further results from the 1950-51 Canadian Sickness Survey, presenting data on the estimated incidence and prevalence of illness in Canada during the survey year. Other sections of the chapter review the activities of the Department of National Health and Welfare, provincial and municipal health services, federal and provincial public welfare and social security programs, the work of the national voluntary health and welfare agencies, veterans' health and welfare services, and hospitals and related institutions.

WHITLA'S DICTIONARY OF MEDICAL TREATMENT. R. S. Allison, Queen's University, Belfast, and T. H. Crozier, Royal Victoria Hospital and Belfast City Hospital. 854 pp. Illust. 9th ed. Baillière, Tindall and Cox, London; The Macmillan Company of Canada Limited, Toronto, 1957. $8.95.

This book is a valuable aid to the general practitioner. All phases of illness are covered with a necessarily sketchy outline of signs, symptoms and diagnostic procedures. The therapy aspect of illness, however, is well covered and in considerable detail.

The subject matter covers a wide scope of diseases, including tropical diseases, proper emphasis being placed on the more common conditions encountered in day-to-day practice. There are good sections discussing an adequate general approach to a patient by a general practitioner and the attempts he may make to combat some of the commoner psychoneuroses.

The methods of treatment are well up to date, and this book should be of great assistance as a reference manual in any general practitioner's office.

STRESS AND STRAIN IN BONES. Their Relation to Fractures and Osteogenesis. F. Gaynor Evans, Wayne University College of Medicine, Detroit, Mich. 245 pp. Illust. Charles C. Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $7.25.

This slender book brings together much material available in many scattered papers, some of the best of them written by the author and his colleagues (Gurdjian, Webster and Lissner) at Wayne University. The emphasis is on engineering principles and techniques but the author successfully translates these for the medically trained reader. Nonetheless, after reading the book, this reviewer strongly felt that few really fundamental and significant points have been firmly established in this controversial field. Rather, it is apparent that most of the methodical and somewhat colourless work already done is spotty and very debatable, at best, and that much more scientific research is necessary.

Obviously, research workers and surgeons dealing with bone cannot ignore this book but the general reader is not likely to find it either very useful or exciting.

SYNOPSIS OF PATHOLOGY. W. A. D. Anderson, University of Miami School of Medicine. 829 pp. Illust. 4th ed. The C. V. Mosby Co., St. Louis, Mo., 1957. $8.75.

This small book was first published in 1942, and is now in its fourth edition, the third having been published in 1952. In the present edition, the general plan is unchanged, but revision and additions have been made in all chapters, bringing the work up to date. As with all single-author texts of such large scope, this revision has been more thorough in some sections than others. The section on "Disturbances of Growth", for example, is essentially unchanged from the previous edition.

The author's style is lucid and the book is easily read, remarkably so considering the amount of material and the size of the book. This edition continues the high standard set by the previous ones, and is heartily recommended to undergraduates and particularly graduates as an excellent synopsis of the subject.

CLASSICS IN ARTERIAL HYPERTENSION. Arthur Ruskin, University of Texas. 358 pp. Illust. Charles C Thomas, Springfield, Ill., 1957; The Ryerson Press, Toronto. $10.50.

The practical daily application and interpretation of medical techniques does not require any knowledge of the history of their development, but if we are to rise above the level of high-grade technicians, surely physicians ought to show a greater interest than do many in the background of our present methods of diagnosis and concepts of disease. This worthy objective has been served in some fields and the idea might profitably be extended to many more. This volume portrays the historical development of the concept of hypertension by reprinting significant contributions (translated into English where necessary, with one exception), of the past 300 years. These reprints are in two groups. The section on "Methods" ranges from Hales through Poiseuille, Riva-Rocci to Korotkov. The section "Significance" includes articles by Aurelianus, Bright, Traube, Potain, Ambard and Goldblatt. For the historically minded, this is recommended reading.

MEDICAL NEWS *in brief*

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CLINICAL PATHOLOGY

The metabolism of iron has been a puzzling problem for many years. Although far from being solved, it has nevertheless received a considerable degree of attention in the main medical centres of the world. The following is an account of the latest developments in this field, gathered at recent meetings in the U.S.A. (such as the Symposium on Iron in Clinical Medicine, San Francisco). These notes have been prepared specially for this Journal by Dr. N. K. de Leeuw of the Royal Victoria Hospital, Montreal, P.Q.

IRON IN CLINICAL MEDICINE

On January 28 and 29, 1957, an International Symposium on Iron Metabolism was held at the University of California School of Medicine, San Francisco, California.

After a historical introduction by Dr. J. B. de C. M. Saunders, the series of lectures was opened by Dr. Carl V. Moore, who reviewed the *Etiology of Iron Deficiency Anæmia.*

Iron deficiency may be due to: (1) excessive loss of iron from the body, (2) poor intake or poor absorption of iron, (3) a combination of (1) and (2).

Iron is excreted in small, but still significant amounts, in urine, fæces and sweat.

Studies with Fe^{59} have shown that the daily fæcal excretion of iron in the normal is 0.3 to 0.5 mg. The source of fæcal iron may be secretion from the mucosa of the gastro-intestinal tract, bile or desquamated duodenal cells. Less than 0.5 g. of iron is excreted daily in sweat. The total daily loss in men is less than 1 mg. per day, in women 1.5 to 2 mg. per day.

Studies with Fe^{59}-containing foods have shown that with rare exceptions normal subjects absorb less than 10% of iron in food. Patients with iron deficiency anæmia have increased absorption of iron. Absorption of food iron is increased by the addition of ascorbic acid, probably because of reduction of iron to the ferrous form.

The diet in the United States contains approximately 12 to 30 mg. of iron, of which approximately 0.6 to 1.5 g. is absorbed. Approximately 12% of the iron contained in iron enriched bread is absorbed.

During growth the body assimilates 4.5 g. of iron, which is 225 mg. of iron per year, or 0.6 mg. of iron per day. Thus, the growing child needs, in addition to the normal iron requirements, 0.6 mg. of iron per day. It is obvious from these figures that a normal female and a growing child are in a precarious state of iron balance, and that iron deficiency is likely to develop in these two groups. That chronic loss of even small amounts of blood may lead to iron deficiency is evident if one realizes that the loss of 2 to 4 c.c. of blood per day equals a loss of 0.8 to 2 mg. of iron daily. This amount of blood may not be detectable in the stool with the usual measures.

Dr. Carl-Bertil Laurell (Sweden) discussed *iron transport* and *haptoglobin.* The iron binding protein called "transferrin" makes up 3% of the total serum proteins, and moves with the beta globulins. The protein can be demonstrated with immunological techniques. Transferrin combines with two atoms of trivalent iron. There exists an equilibrium between the trivalent iron ions and transferrin on one side and the iron-transferrin complex on the other side.

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The ratio of transferrin to trivalent iron and the pH of the capillary blood probably are important factors in the movement of iron across capillary membranes.

Studies seem to indicate that iron leaves the plasma as trivalent iron and not as iron-protein complex. Approximately 10 to 20% of transferrin is replaced per day. The mechanism responsible for regulation of the transferrin level is not known.

*Haptoglobin.** — French investigators discovered several years ago that a protein in plasma combines with hæmoglobin. The level of the hæmoglobin-protein compound in plasma was determined with ethyl peroxide and was called *the "peroxidase index of plasma"*. Dr. Laurell has studied the nature and properties of this protein, now called *haptoglobin,* and it was found to have a molecular weight of 170,000, electric mobility with the alpha$_2$-globulins, an isoelectric point of 4.1, and a sedimentation constant S_{20} equal to 4.1. Haptoglobin may appear in different forms in the plasma, as a monomer or as a dimer or polymer and is a mucoprotein. The globin part of hæmoglobin is linked to the haptoglobin. Since hæmoglobin and haptoglobin have different electrophoretic mobility, the hæmoglobin binding capacity of serum can be determined by adding increasing amounts of hæmoglobin to serum and subjecting the mixtures to paper electrophoresis. When haptoglobin is saturated, two different bands will be seen, one of the haptoglobin-hæmoglobin compound and one of free hæmoglobin.

At normal blood pH, 90 mg. of hæmoglobin may be bound by haptoglobin. The hæmoglobin-haptoglobin complex is a large molecule, which cannot be excreted by the kidney. In a hæmolytic crisis there is too little haptoglobin to bind all of the released hæmoglobin, so that free hæmoglobin is now excreted by the kidneys. The concentration of haptoglobin in plasma determines the so-called "renal threshold" for hæmoglobin.

In vivo experiments show that after saturation with hæmoglobin there is, over a six-hour period, a gradual disappearance of the hæmoglobin-haptoglobin complex, which is taken up by the reticulo-endothelial system, followed by a slow regeneration of the

*Information obtained from a lecture on Haptoglobin held in Seattle, Washington, is included in this review.

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MEDICAL NEWS *in brief*

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alpha$_2$-protein during the following days. The haptoglobin concentration is increased in leukæmia, hæmolytic anæmia, and pernicious anæmia. Low concentrations are found in cirrhosis of the liver.

Dr. L. Heilmeyer's lecture on *Ferritin* has been reviewed earlier in this journal.

Transplacental Iron Transport—Dr. Clement Finch.

Experiments in rabbits show that the amount of fetal iron increases with the weight of the fetus. Towards the end of pregnancy the plasma iron turnover in the pregnant rabbit decreases, whereas the fetal iron turnover increases. Infection in pregnant rabbits gives a decrease of iron turnover in mother and fetus, whereas the addition of supplemental oral iron will cause an increased turnover in both mother and fetus. It is of interest that the maternal plasma iron is lower than the fetal plasma iron in both human and rabbit. Transfer of iron through the placenta is very rapid and takes place only in one direction, i.e. from the mother to the fetus. The iron can be demonstrated in what appear to be the tips of the villi of the placenta. Even after the fetus has been removed, the placenta still takes up radioactive iron. These studies show the ability of the placenta to take up iron, but the transfer of iron is related to the size of the fetus and not to the size of the placenta.

In the human, the same general relationship exists between growth, weight and iron content of the fetus. The amount of iron transferred through the placenta is as follows: 1st trimester, 0.5 mg.; 2nd trimester, 7.5 mg.; 3rd trimester, 312.5 mg. This means that at the end of pregnancy there is an additional requirement for the mother of 4 mg. of iron per day. It is suggested that in the human the mechanism of iron transfer through the placenta is similar to that in the rabbit.

Iron kinetics were discussed by Dr. M. Pollycove. Iron in the *bone marrow* is divided into two compartments: (1) *the erythron,* containing 30 mg. of iron, and (2) *a labile pool* containing 100 mg. of iron. One-third of the iron entering the bone marrow is returned to the plasma. *The red cell mass* contains 2700 mg. of iron; *plasma* contains 4 mg. of iron, and *storage iron* is 1000 mg. When radioactive iron is injected intravenously, the concentration of radioactive iron of the plasma does not fall off in a straight line to zero, and the curve depicting this is divided into two parts: The initial steep slope of the curve permits calculation of the total daily removal of iron from the plasma, whereas the second, more shallow, part of the slope represents a continuous return of radioactive iron into the plasma from the labile pool of the bone marrow. The first part of the curve is completed at about six hours, whereas even after 11 days the shallow part of the slope can still be followed.

Extrapolation back to zero of the shallow part of this curve permits determination of the total amount of iron in the labile pool of the bone marrow, which is approximately 90 mg. of iron.

Dr. Pollycove has estimated that the amount of iron leaving the plasma is 36 mg. per day; iron used for hæmoglobin formation is 22 mg. per day, and the normal mean red blood cell life span equals

$$\frac{\text{total hæmoglobin}}{\text{daily hæmoglobin loss}} = 122 \text{ days.}$$

With multiple counters placed over the liver, spleen, and the bone marrow, the uptake in these organs can be demonstrated. When the rate of uptake of radio-iron in the bone marrow and the rate of uptake of radio-iron in the red cell mass are plotted on the same scale, their time interval permits determination of the *"mean*

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erythron hæmoglobinization time". Normally this is 1.4 days.

In *hæmochromatosis*, radioactive iron disappears from the plasma in a different way. There are three components to the curve indicating three pools of iron. The labile iron pool in the bone marrow is increased in this condition.

In *iron deficiency anæmia* the hæmoglobin synthesis is decreased and the mean life span of the red cell with this method was found to be 44 days, which would suggest that there is a hæmolytic component to the anæmia of the iron deficiency state. Surprisingly enough, the "*mean erythron hæmoglobinization time*" in this condition was found to be increased to 2.8 days. In hæmolytic states and in *pernicious anæmia*, as could be expected, there is a marked return of iron from the labile bone marrow pool back to the plasma.

The Iron Requirements in Infancy were discussed by Dr. Philip Sturgeon.

At the age of four months the serum iron is low, and then rises slowly, so that at six months the serum iron is only slightly lower than normal (approximately 64 μg. %) with an increased unsaturated iron binding capacity. At the age of one year, the red blood cell is microcytic and hypochromic, and the condition is called "physiological anæmia of late infancy". When at this time iron is given, there is an increase in hæmoglobin. It was concluded from these studies that in the case of normal children there is usually not enough iron in the food. The addition of 0.5 to 1 mg. of iron per kg. per day was followed by an optimal improvement in hæmoglobin.

Problems of the Premature—by Dr. I. Schulman.

Premature show a fall of hæmoglobin on two occasions: (1) at approximately the 50th day and (2) at the 150th day. For evaluation of the anæmia of prematures, determinations of total hæmoglobin mass were carried out, and it was shown that there is a fall in total hæmoglobin mass until the 50th day, at which point a reticulocytosis takes place, followed by a slow increase in hæmoglobin mass until the 130th day. Then then there is a fall again, the lowest level being reached at approximately the 150th day. When treatment with iron is given at this point, there is a rise in hæmoglobin mass. The first fall of hæmoglobin mass is due to decreased erythropoiesis and a shortened life span of the red blood cell, and it does not respond to iron therapy. The time interval after birth at which the second drop in hæmoglobin mass takes place is not constant in prematures, but depends on (1) the size of the hæmoglobin mass at birth, (2) the rate of weight gain of the premature and (3) other factors.

Iron Absorption in Infants—by Dr. N. J. Smith.

Causes of iron deficiency in infants are (1) blood loss, (2) inadequate diet, (3) inadequate iron stores at birth, and (4) gastro-intestinal disease.

The iron stores of infants are low. If Fe^{59} labelled cow's milk was given to adults and infants, both groups absorbed approximately 10% of the labelled iron.

In contrast to Dr. Sturgeon's estimations, Dr. Smith's calculations seemed to indicate that the iron supply in an optimal diet for a normal infant is adequate, but in any situation in which there is increased iron loss or decreased absorption, the balance can become negative.

Acute Iron Toxicity—by Dr. R. A. Aldrich.

Acute iron toxicity occurs mostly in small children (80% of those affected are between 12 and 24 months of age). The mortality rate is 45%. The fatal dose ranges from 4.8 to 18 g. After poisoning with ferrous sulfate the infant soon vomits a dark brown

or bloody liquid and complains of abdominal pain, followed by the passing of liquid black or greenish stools. Shock develops, with cyanosis, drowsiness and Kussmaul's respirations. Death may occur in less than six hours. The child may wake up and come out of shock. It may then either recover or relapse into shock, become comatose and die. A complication following recovery is scarring of the pyloric end of the stomach with stenosis. The serum iron in these patients may reach high levels. Biochemical changes are due to fluid loss caused by diarrhœa and blood loss. The CO_2 combining power is lowered. There is a marked leukocytosis. The blood *is incoagulable* due to so far undetermined cause. The cyanosis does not clear with oxygen administration. Jaundice occurs in some cases but is not explained. *Treatment* includes (1) induction of vomiting and aspiration of stomach contents with a large bore tube, after rinsing with an alkaline solution to dissolve the enteric coating of the tablets. (2) It is suggested that a flat plate of the abdomen be taken to see if a large number of tablets are in the bowel, in which case laparotomy may be considered. (3) Exchange transfusions may be helpful. (4) Use of sodium versenate and BAL is not generally recommended.

Parenteral Iron Therapy--by Dr. R. O. Wallerstein.

Oral therapy with iron has the following disadvantages: (1) it takes a long time before response is apparent; (2) it may cause gastro-intestinal upset; (3) body stores are usually not replaced by this method of treatment. Iron dextran, or Imferon, has now been used intramuscularly and seems almost free of side reactions. Dosage for children with iron deficiency is as follows:

Less than 6 months: 100 mg. of elemental iron

6-12 months: 200 mg. of elemental iron

12-24 months: 300 mg. of elemental iron

24-36 months: 400 mg. of elemental iron.

The hæmoglobin response in a three-week period showed great variation. The reticulocyte response after five to seven days ranged from 9 to 21%. Twelve to 72 hours after treatment was started, hæmosiderin could be demonstrated in the bone marrow. A hæmoglobin rise of less than 2 g. in three weeks as response to treatment suggests another etiology of the anæmia and not iron deficiency.

Pharmacology of Parenteral Iron Preparations—by Dr. L. Goldberg.

If large doses of iron dextran (Imferon) are injected intravenously into experimental animals, a slight anticoagulant and hæmolytic effect is observed. No ill effects result except organ siderosis. Imferon will not precipitate until the pH is 6 or less and is in all these respects superior to saccharated oxide of iron.

Metabolism of Dextran in Experimental Animals.—After intramuscular injection, the molecules are rapidly taken up by the local macrophages, or transferred via the lymphatics to the regional lymph nodes, from which they are transported to the blood stream and then to the reticulo-endothelial system. Here dextran and iron dissociate. Dextran is metabolized and execreted partly by the kidneys. Iron is released into the blood stream and is then bound to transferrin and carried to the bone marrow, to be utilized in erythropoiesis. A small amount of the iron is excreted through the liver, in the form of ferritin, into the bile and little is excreted into the urine. The intramuscularly injected iron should not be considered as depot iron since the reticulo-endothelial

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system is the true depot for iron therapy. Absorption from the intramuscular site may be depressed (1) when lymph flow is slowed down or (2) when in recumbency the material sinks down between the fascial planes, or in fat tissue.

In man, intravenously injected Imferon gives high iron levels, but the iron binding capacity is unchanged since the iron is bound to dextran. The iron is then transported to the reticuloendothelial system. It is dissociated and the iron as such is now released into the blood and bound to transferrin so that the unsaturated iron binding capacity is at this point decreased. The iron is transported to the bone marrow. If large amounts are given, some of it will go to the liver cells.

Overdosages of Imferon in Animals.—In the *rabbit,* injection of 825 mg. of iron per kg. will cause a nephrotic syndrome within a few weeks. Recovery usually takes place. In the early stages of this illness iron can be demonstrated in the glomeruli and in the tubules. If recovery takes place, the iron is withdrawn from the glomerular capillaries. Only siderosis of the internal organs remains. In animals that have died, *thrombotic* lesions have been demonstrated in the glomerular capillaries. In *rats,* with doses of 900 mg. per kg. body weight, different pathological changes take place, resembling vitamin E deficiency although they are not necessarily identical. It is to be noted that dextran without iron will not give these changes.

The Treatment of Iron Deficiency—by Dr. A. R. Stevens.

The oral dose which gives optimum response is 60 mg. of elemental iron t.i.d., which is 1-2 mg. per kg. body weight. When this dose, given in the ferrous form, is combined with ascorbic acid (100-1000 mg./dose) 30% better absorption is obtained.

Response to Oral Iron Treatment is considered adequate if in three weeks' time there is a rise of hæmoglobin of 2 g. and a rise of hæmatocrit of 5%. Failure to respond may be due to (1) incorrect diagnosis, (2) complicating disease (infection), (3) active bleeding, (4) failure to take medication, (5) failure to absorb iron from the gastro-intestinal tract, which is considered rare.

Parenteral Iron Therapy with Imferon.—In over 500 cases there were only two reactions (generalized joint aching and generalized urticaria). In children, the usual dose given is 300 to 400 mg. of Imferon; in adults, 1500 to 2000 mg. *Indications* for parenteral iron therapy are (1) intolerance to oral iron, (2) gastro-intestinal inflammatory disease, (3) the creation of iron stores in a chronic bleeder, (4) poor absorption as in sprue and myxœdema, and (5) an unreliable patient.

The hæmatocrit and hæmoglobin increase three weeks after Imferon treatment is the same as for oral iron therapy.

Iron Deficiency Anæmia of Pregnancy—by Dr. C. J. Lund.

The estimated need of iron during pregnancy is calculated to be 1200 mg. of iron, that is 4 mg. per day.

The increase of plasma volume at 36 weeks of pregnancy shows a great variation in normal women. Dr. Lund therefore divides the pregnant women into hypovolæmic, isovolæmic and hypervolæmic. The groups have the following plasma volume in c.c. per kg. body weight: hypovolæmic less than 55, isovolæmic from 55 to 75, and hypervolæmic from 80 to 100 c.c. per kg. He stresses the point that it is of value to determine red cell mass and plasma volume in order to determine whether a particular pregnant woman is anæmic, since hypovolæmia may mask anæmia and on the other hand hypervolæmia may be responsible for a "so-called anæmia". The author considers serum iron determinations of limited value in the diagnosis of iron deficiency anæmia of pregnancy, but he finds the determination of the free erythrocyte protoporphyrin a greater help in diagnosis.

Parenteral Iron in Pregnancy—by Dr. L. A. J. Evans.

The speaker stressed the point that Imferon should be given *intramuscularly,* and that a 2½-inch needle should be used—an even longer one for obese patients. If single doses of 1500 mg. of Imferon are given, the patient should be hospitalized. It was advised to draw the skin downwards before injecting Imferon, to prevent the formation of a skin tract. Warning was given against *subcutaneous* injections since the iron is *not absorbed* from subcutaneous sites and causes *local melanin formation* with deep brown staining of the skin. In many patients weekly smaller injections were given. *Reactions* to Imferon were: slight increase in temperature; increased pulse rate; albuminuria during the time of the iron-dextran injections (2 cases); a punctate rash (one case); urticaria (one case).

Some Aspects of Copper Metabolism—by Dr. George E. Cartwright.

When pigs are fed with a copper deficient diet, an anæmia develops which is microcytic and hypochromic. The bone marrow becomes hyperplastic and normoblastic. The anæmia is accompanied by a low plasma copper and low serum iron with an increase in the unsaturated iron binding capacity. The red cell copper content is one-third of normal. Iron metabolism in copper deficient pigs is affected as follows: there is a decrease of tissue iron in the copper deficient animal in spite of added dietary iron. If iron is also withdrawn, treatment with copper gives no cure of the anæmia, but treatment with iron plus copper gives an improvement of the anæmia. It is thus shown that the absorption of iron is impaired in copper deficient animals.

The survival time of red blood cells of copper deficient animals as measured by Fe^{59} is shortened, a finding which was confirmed with the use of the Cr^{51} method. When red cells of copper deficient animals are transfused into copper deficient animals, they show a shortened survival time, but when they are transfused into a normal animal, a more nearly normal survival time is obtained. The metabolic defects in copper deficient animals may be summarized as follows: (1) There is a deficiency of ceruloplasmin (copper binding protein in plasma), of cytochrome oxidase of the heart, and of erythrocuprin (copper containing protein in red cells). (2) There is a decreased ability to absorb iron from the gastro-intestinal tract. (3) There is a decreased life span of the red blood cells. (4) There is an impaired ability of the bone marrow to increase production.

Hæmosiderosis versus Hæmochromatosis was discussed by Dr. M. S. Kleckner and Dr. M. Block.

Both speakers divide hæmochromatosis into (1) primary and (2) secondary type occurring in a younger age group, associated with refractory anæmia in which the number of transfusions apparently is not related to the development of hæmochromatosis. Necropsy findings are identical in both cases.

Dr. Matthew Block believes that hæmochromatosis is due to increased iron absorption, with an abnormal reaction to it in the tissues. He feels that the majority of patients with hæmosiderosis do not develop hæmochromatosis.

Dr. Finch remarked that in primary hæmochromatosis the iron goes into the liver cells, the pancreas and the heart. He said that in these pa-

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tients it would seem that iron escapes the reticulo-endothelial system. To him the element of time seems important in the development of hæmochromatosis.

TETANUS IN A BRITISH HOSPITAL

In a large general hospital in the Midlands of England, the North Staffordshire Royal Infirmary, Stoke-on-Trent, five patients developed tetanus after an operation. Two of these patients have since died and the other three have recovered. Bacteriological study of the operating-theatre block which contained three theatres and their ancillary departments revealed tetanus spores in samples of dust, debris and wall plaster from the floor of the main theatre corridor, and from various other locations in the block. Spores were found in general floor sweepings from the theatre block, in a storage box for rubber gloves, and on a surgeon's glove contained in a sterilization drum. The catgut used was not incriminated. The hospital management committee has decided not to reopen the present theatre block at the Infirmary, but to build new theatres at a cost of $100,000.

AMERICAN HEART ASSOCIATION AWARDS

During April the American Heart Association announced awards to 155 scientists for research in cardiovascular disease. The total amount awarded is $977,000, and awards run from July 1, 1957, for 12 months. The new awards provide differing levels of support, through lifetime career investigatorships, established investigatorships for five years and research fellowships for one or two years.

Many of the research problems tackled will be related to the development of atherosclerosis, especially in relationship to dietary fat. New types of anticoagulant are also under study. Studies of the relationship between streptococcal infections and rheumatic fever will also be undertaken. Some investigations will be concerned with cardiovascular surgery.

CANADIAN LIFE INSURANCE FELLOWSHIPS

Financial assistance from the Canadian Life Insurance Fellowship Fund has been granted to 15 medical research projects at 10 medical schools of Canadian universities. The aggregate amount awarded by the fund this year is over $60,000 and the individual fellowships range in value from $2500 to $6000.

Ten of the 15 projects are new investigations being undertaken by medical scientists, while the other five are renewals from the previous year.

Receiving fellowships this year are the following:

University of Alberta: Dr. E. C. Elliott for a continuation of his studies in extracorporeal circulation, myocardial re-vascularization and replacement of blood vessels and heart valves.

University of British Columbia: Dr. J. D. E. Price for studies of sodium excretion in normotensive and hypertensive humans.

Dalhousie University: Dr. D. J. Dodds for studies on intermediary metabolism of fat and carbohydrate in human obesity.

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Laval University: Dr. B. Belleau for a continuation of his research on chemotherapy of hypertension.

University of Manitoba: Dr. A. Zipursky for studies on the erythrocyte phosphorus metabolism in normal people and in patients with acquired hæmolytic anæmia.

McGill University: Dr. C. J.-P. Giroud for a continuation of his studies on aldosterone and other corticoid hormones; Dr. J. B. Dossetor for research on factors influencing the rate of electrolyte excretion in health and disease; Dr. A. Taussig for research on biosynthesis of viruses and of virus components.

University of Montreal: Mr. R. Nadeau for studies on the role of P^{32} incorporation in phosphorus esters in the heart muscle of the aged rat after exercise.

Queen's University: Dr. L. S. Valberg for a continuation of his studies on acute massive liver necrosis.

University of Toronto: Mr. H. Salem for studies on the effects of possible atmospheric pollutants on the respiratory system; Dr. G. F. Buckley for research on the extent and nature of arteriosclerosis in peripheral gangrene; Dr. A. Rapoport for a study of metabolic changes in patients with carcinoma of the breast before and after hypophysectomy.

University of Western Ontario: Dr. C. R. Engel in connection with his research on steroids and related products; Dr. N. M. Lefcoe for a critical evaluation of some of the commonly used tests to measure the efficiency of the workings of the lungs.

THE POSTGRADUATE MEDICAL SCHOOL OF LONDON

The only medical school in the Commonwealth designed entirely for postgraduate work is appealing for $750,000. The Postgraduate Medical School of London, England, will use these funds for long-needed expansion.

In 1921 the Athlone committee recommended "the institution of a postgraduate medical school attached to a large and well-equipped hospital". In 1930 the Hammersmith Hospital was converted into a postgraduate teaching hospital of 500 beds and a medical school with residences. The school was granted a Royal Charter in 1931. Because of a financial crisis only £200,000 was available instead of the expected £500,000. Nevertheless, in 1935 the school was officially opened. Since then, 12,000 qualified doctors have attended the school, of whom over 5000 came from outside the U.K. During World War II refugee doctors were acclimatized, some undergraduates were trained, and courses were held for serving medical officers in the medicine and surgery of war. In the post-war years, war damage to the hospital was repaired (there are now 694 beds), a building to house the cyclotron of the Medical Research Council was constructed, and new laboratories were built on top of existing school buildings. Last year a new unit for investigating metabolic disorders was opened. In 1947 the library was taken over as a laboratory and the books were temporarily placed in a prefabricated hut. They are still there.

Under the National Health Service Act, the Hammersmith Hos-

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pital was joined with the West London Hospital and St. Mark's Hospital as a teaching unit with the same board of governors. In 1945 the creation of the British Postgraduate Medical Federation placed postgraduate education on a more stable basis. The Postgraduate Medical School, along with various specialist institutes in London, is an institute of the Federation.

The School has played a prominent part in research as well as education. Cardiac catheterization was pioneered at the school, which also took a lead in developing liver biopsy. Contributions have been made in the fields of renal disorders, hypertension, anæmia, silicosis, the relationship between blood groups and disease, and the use of heart-lung machines in cardiac surgery.

The School must exist solely on a university grant of £200,000, which cannot cover the cost of expansion. It is hoped that the school may be expanded, and an up-to-date core of laboratories and lecture theatres capable of further expansion may be provided. Two separate buildings are needed, one for activities involving large groups of people, the other for small study and research groups. A bridge connecting the two buildings will house the library, the dean's suite of administrative offices and three lecture theatres.

Contributions to the Appeal Fund should be made payable to the "Postgraduate Medical School Extension Fund" and sent to the Appeal Treasurer, Postgraduate Medical School, Ducane Road, London, W. 12.

SARCOIDOSIS INVESTIGATION

A project sponsored by the United States' Veterans' Administration has recently been started to investigate the etiology of sarcoidosis. Five hospitals will contribute information on the environment, occupation, eating habits and self-medication of patients affected by this disease. The central office research team is made up of Dr. M. M. Cummings, Director of Research Service; Dr. Edward Dunner, Secretary of the Veterans' Administration Armed Forces' Committee on Chemotherapy of Tuberculosis; Dr. R. H. Schmidt, Jr., Tuberculosis Service, and J. H. Williams, of Research Statistics. These men have been connected with the investigation of sarcoidosis since 1954. So far, 1700 cases of sarcoidosis have been diagnosed in these hospitals between 1949 and 1956. A similar study has been under way for the last few years in hospitals of the Canadian Department of Veterans' Affairs.